# AZOLES AND BENZAZOLES
# SYNTHESIS, REACTIVITY AND THEIR APPLICATIONS IN ASYMMETRIC SYNTHESIS

By

DIANA CRIMHILDA ASLAN

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1998

*To my parents*

*If you can trust yourself when all men doubt you*
*But make allowance about their doubting too...*
*(Kipling)*

ACKNOWLEDGEMENTS

First and foremost I wish to thank my supervisor, Professor Alan R. Katritzky for his guidance and encouragement throughout the course of this work, especially for helping me grow as an organic chemist. His energy and organization will always be an inspiration for me.

I would like to thank the members of my supervisory committee, Dr. Eric Enholm, Dr. John Reynolds, Dr. Dinesh Shah, and Dr. Robert Hanrahan for their time spent, insight and advice. I would also like to thank Dr. Deyrup for his guidance and advice from day one.

Special thanks go to my teachers at the University of Florida especially to Dr. Eric Enholm for his excellent organic synthesis class and Dr. Roy King for challenging me in the "mysteries" of organic spectroscopy (with a touch of humor).

I want to acknowledge all my group leaders for their suggestions during the preparation of this work: Dr. Irina Shcherbakova, Dr. Peter Leeming, Dr. Daniela Oniciu and Dr. Dorin Toader. I would also like to thank Dr. Ion Ghiviriga for all his help.

I will always cherish Petia's friendship and thank her for being there.

I am grateful to Dorin for generously sharing the benefit of his knowledge and experience with me, for motivating my ambition and for standing by me in good and rough times.

Last but not least, my deepest thanks go to my wonderful parents for their love and encouragement, for instilling me the desire to go further and never give up.

TABLE OF CONTENTS

page

ACKNOWLEDGEMENTS ..... iii

ABSTRACT ..... vi

CHAPTERS

1 GENERAL INTRODUCTION

2 SYNTHESES AND TRANSFORMATIONS OF SUBSTITUTED BENZAZOLYL-(BENZOTRIAZOL-1-YL)METHANE ..... 4

2.1 Introduction ..... 4
2.2 Results and Discussion ..... 8
2.3 Conclusions ..... 16
2.4 Experimental Part ..... 17

3 SELECTIVE REACTIVITY OF $SP^3$ AND $SP^2$-CARBANIONS OF 1-SUBSTITUTED 1,2,4-TRIAZOLES ..... 29

3.1 Introduction ..... 29
3.2 Results and Discussion ..... 32
3.3 Experimental Part ..... 36

4 ASYMMETRIC INDUCTION USING CHIRAL 1,2,4-TRIAZOLE AND BENZIMIDAZOLE DERIVATIVES ..... 44

4.1 Introduction ..... 44
4.2 Results and Discussion ..... 46
4.3 Experimental Part ..... 54

5 ASYMMETRIC SYNTHESIS OF 2-(α-HYDROXYALKYL)-BENZIMIDAZOLES ..... 66
5.1 Introduction ..... 66
5.2 Results and Discussion ..... 68
5.3 Conclusions ..... 72
5.4 Experimental Part ..... 74

6 ALKYLATION OF BENZOTRIAZOL-1-YL ALKYL AND ARYL SULFOXIDES ..... 84

6.1 Introduction ..... 84
6.2 Results and Discussion ..... 91

6.3 Conclusions ..... 100
6.4 Experimental Part ..... 100

7 GENERAL CONCLUSIONS ..... 107

REFERENCES ..... 109

BIOGRAPHICAL SKETCH ..... 117

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

AZOLES AND BENZAZOLES
SYNTHESIS, REACTIVITY AND THEIR APPLICATIONS IN ASYMMETRIC SYNTHESIS

By

Diana Crimhilda Aslan

May, 1998

Chairman: Alan R. Katritzky
Major Department: Chemistry

2-(1-Methylbenzotriazolyl)benzazoles were synthesized *via* the condensation between *o*-substituted anilines and the corresponding carboxylic acid derivative under acidic conditions (polyphosphoric acid). These methylene bisbenzazoles readily form the anion on reaction with *n*-BuLi and subsequent reactions with alkyl iodides to give the corresponding mono- or di-alkylated derivatives; reactions with electrophiles other than alkyl iodides (α-bromoacetophenone, benzophenone, ethyl benzoate, carbon disulfide) did not occur. 2-(1-Methylbenzotriazolyl)benzazoles are shown to react with aromatic aldehydes by aldol-type condensation to give β,β-dibenzazolo-substituted styrenes. The novel compounds obtained are expected to possess biological activity (anti-viral, anti-bacterial).

A study of selective reactivity of $sp^2$ and $sp^3$-carbanions of N-alkyl-1,2,4-triazoles was performed. These substrates were lithiated and subsequently reacted with $D_2O$ (or $H_2O$), alkyl iodides and benzophenone, by different standardized procedures of

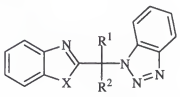
lithiation/treatment with electrophile. These procedures were aimed at the elucidation of the regioselectivity of the first and subsequent lithiations, along with the determination of the regioselectivity of the ambident carbanions in their reactions with electrophiles.

Novel spiro-fenchyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole and 1*H*,3*H*-oxazolo-[3,4-*a*]benzimidazole were synthesized using 1(*R*)-fenchone and *S*-lactic acid as sources of chirality. 5-Substituted 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles were obtained with excellent diastereselectivity and were converted into 2-(α-hydroxyalkyl)benzimidazoles in high yields, thus providing an efficient approach to stereoselective synthesis of these derivatives as pure *D*-enantiomers.

A brief study of asymmetric synthesis and alkylation of benzotriazol-1-ylmethyl sulfoxides was undertaken and the results were compared with those published for other classes of sulfoxides.

# CHAPTER 1
# GENERAL INTRODUCTION

2-Substituted benzoxazoles are of increasing importance in the chemical industry and biochemistry, being also used as masked carbonyl synthons for various syntheses. Although methods for the preparation of these compounds have been intensively studied, methylenebisbenzazoles having two different heterocycles linked by a methylene group have not been previously synthesized. Chapter 2 presents a straightforward method to obtain these compounds along with the attempted benzotriazole displacement using Grignard reagents.

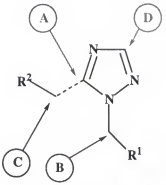


X = S, O, NH
$R^1$, $R^2$ = alkyl

Scheme 1.1

In many of their applications, 1,2,4-triazoles are used as efficient synthetic precursors, yet the reactivity of N-alkyl substituted 1,2,4-triazoles is far less studied. A new study of selective reactivity of $sp^2$ and $sp^3$-carbanions of 1-substituted 1,2,4-triazoles is described in Chapter 3, including only the experiments and results obtained by this author. As a starting point of this study, one can examine the few possible reactive sites for the first and consecutive alkylations (marked A, B, C and D in Scheme 1.2). The

experiments were designed to determine the order of reactivity depending on the nature of N-alkyl group.

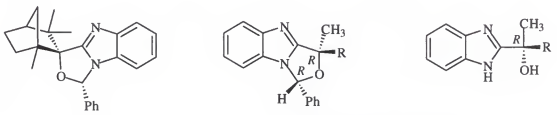



Scheme 1.2

The most common examples of diastereoselective reactions are those that aim to the formation of additional stereogenic centers in an achiral substrate. The strategies employed require the presence of stereogenic elements that would exert an unambiguous steric bias to the environment of the reaction site and a sufficient difference (min. 2 kcal) between the free energies of the possible diastereomeric products (thermodynamic control) or the transition states leading to them (kinetic control) [94MI1]. These cases involve mainly cyclic or polycyclic molecules with limited conformational freedom. The less feasible tasks are associated with acyclic or mobile substrates.

Small heterocyclic rings like oxazolidine have limited flexibility, especially when fused with other heterocycles (imidazole, benzimidazole) and offer relatively rigid systems for elaborating new chiral centers. Steric control can be achieved by converting an acyclic substrate (e.g. chiral benzimidazole) into a bicyclic derivative (oxazolobenzimidazole). This concept, formulated by Seebach [96AG2708] as the "self-regeneration of stereogenic centers" can be explained as "a chiral compound containing a single stereogenic center" (chiral benzimidazole in our case) "can undergo stereocontrolled reaction at that center by forming a derivative with a second stereocenter, the configuration of which is determined by that of the original center."

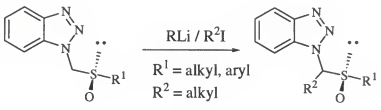
Following this approach, the work presented in Chapters 4 and 5 was aimed at chiral induction of new stereogenic centers in novel chiral polycyclic molecules (Scheme 1.3) and to the formation of chiral acyclic targets (alcohols, aldehydes). The sources of chirality were 1-(*R*)-fenchone and *S*-lactic acid, which are both readily available and inexpensive.



R = Et, Bu, benzyl, allyl

Scheme 1.3

In turn, the major difficulties involved with stereodifferentiating syntheses are associated with conformationally mobile substrates like dialkyl or aryl sulfoxides, the creation of the first stereogenic center and the induction of a second one in an acyclic molecule. As will be shown in Chapter 6, this task can be fulfilled by choosing the appropriate asymmetric oxidizing systems and by designing the substrate in such a way to impose a sufficient rotational barrier between the conformers. Taking into account that the few previous studies of sulfoxide alkylation have drawn contradictory conclusions, our experiments aim to bring more data to the problem and elucidate it for our benzotriazol-1-ylmethyl sulfoxide system.



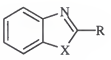

Scheme 1.4

# CHAPTER 2
# SYNTHESES AND TRANSFORMATIONS OF SUBSTITUTED BENZAZOLYL-(BENZOTRIAZOL-1-YL)METHANE

## 2.1 Introduction

Benzazoles (benzimidazoles, benzothiazoles and benzoxazoles) are extremely important heterocycles from an industrial, agricultural and pharmaceutical point of view. For example, it was noted in an early investigation that benzimidazole inhibits the growth of certain yeasts and bacteria [44JBC225]. The discovery of 5,6-dimethylbenzimidazole as a unit in vitamin $B_{12}$ has increased the interest in this class of compounds. A number of alkyl benzimidazoles have been tested and found to possess anti-vitamin $B_{12}$ activity, and some have been reported as anti-viral compounds [53CA11327]. It has been proved that structural modifications can produce marked effects on physiological activity. Some of these compounds exerted strong inhibitory action not only against purine and $B_{12}$-requiring microorganisms but against folic acid-requiring organisms as well [57JCS5706]. A series of unsymmetrically substituted bis-benzimidazoles has been synthesized as analogues of DNA binding fluorochrome Hoechst 33258 [90SC955]. Hoechst 33258 contains potentially GC recognizing groups and it is known to bind in the minor groove of DNA occupying 4-5 base pairs in AT regions. Furthermore, some benzothiazolium and benzoxazolium salts were conceived as heterocyclic analogues of the hypotensive drug Elvetil and pharmacologically classified as non-specific spasmolytics; they were also found to possess interesting activity against dermatophytes and bacteria [63JCS4322]. Several synthetic routes to benzazoles **2.1a-c** are known, some of them are specific for a particular heteroatom **X,** and a few are applicable for all three types of benzazoles. The classification

of the methods can be based on the number of new bonds formed in the process of cyclization (in order to close the benzazole ring).



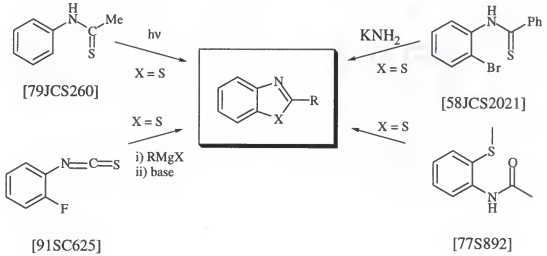
**a**: X = O benzoxazoles
**b**: X = S benzothiazoles
**c**: X = N benzimidazoles

**2.1a-c**

Figure 2.1

2.1.1. Formation of One Bond

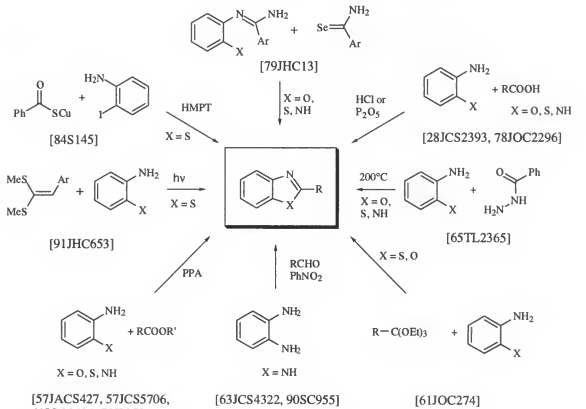
Carbon, nitrogen and sulfur anions are effective nucleophiles in reactions with benzyne derivatives. Nucleophilic attack initiates an addition to the triple bond which is completed by acquisition of a proton [58JCS2021]. A halogenated aromatic ring as an aryne precursor and a conjugated acid of an active nucleophile in a suitably located side chain on treatment with a strong base (such as $KNH_2$ in liq. ammonia) furnish ring closure products and represent intramolecular nucleophilic addition to the aryne structure (Scheme 2.1).




Scheme 2.1

2.1.2. Formation of Two Bonds

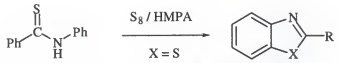
The utility of polyphosphoric acid as a remarkably effective condensing agent, both for intra- and inter-molecular condensations was extensively explored during the years. Thus, the polyphosphoric acid catalyzed condensations proceeded in good yields [57JACS427, 57JCS5706, 61JOC3434, 78JIC531]. The nature or position of inert substituents (such as chloro- or methyl-) in the aromatic acid ring did not appear critical except in the presence of the *o*-nitro group. By the condensation method, bis-benzothiazoles [61JOC3434] and bis-benzimidazoles [57JCS5706] were obtained from dicarboxylic acids and *o*-aminothiophenol and *o*-phenylenediamine. Though the direct condensation provides the most simple route to benzazoles, the method requires high temperatures. A few other synthetic routes to benzazoles are prezented in Scheme 2.2.




Scheme 2.2

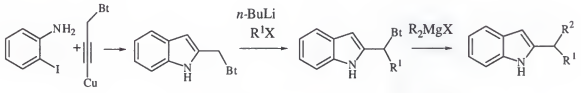
2.1.3. Formation of Three Bonds

The use of elemental sulfur in HMPA was shown to be a convenient thiation reagent for the activated aromatic ring [77ACS203] (Scheme 2.3).



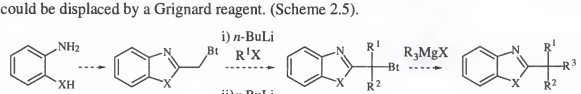

Scheme 2.3

The initial objective of research was to find a method for the synthesis of unsymmetrical methylene bisheterocycles so far unavailable, as well as 2-substituted benzazoles. A previous approach consisted of the synthesis of benzotriazolylmethyl-indole followed by nucleophilic substitution of the Bt group to give 2-substituted indoles [95JOC3401] (Scheme 2.4).




Scheme 2.4

Similarly we could build the benzotriazolylmethylbenzazoles via condensation of the appropriate amine with a carboxylic acid derivative having a Bt group in α position. After introducing 2 alkyl groups through succesive lithiations/alkylations the Bt moiety could be displaced by a Grignard reagent. (Scheme 2.5).



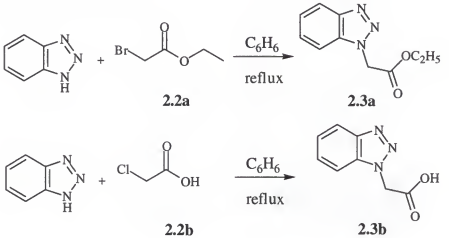

Scheme 2.5

Since the condensation of the carboxylic acid derivatives with the corresponding ortho-substituted anilines in the presence of polyphosphoric acid was reported to give good results in synthesis of benzazoles, we employed this method to prepare 2-(benzotriazol-1-ylmethyl)-benzothiazole, -benzoxazole and -benzimidazole. We have not found any literature examples of the synthesis of this class of bismethyleneheterocycles.

## 2.2 Results and Discussion

### 2.2.1. Synthesis of 2-(Benzotriazol-1-ylmethyl)benzazoles.

As a source of carboxylic acid fragment, we have used ester **2.3a** or acid **2.3b**, which were obtained in 88% and 94% yields, respectively, according to the literature procedures [88CA75308, 95MI1] .



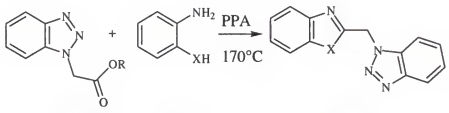

**2.2a** **2.3a**

**2.2b** **2.3b**

Scheme 2.6

Using the previously described condensation method with polyphosphoric acid [57JACS427, 57JCS5706, 61JOC3434, 78JIC531], 2-(benzotriazol-1-ylmethyl)-benzazoles **2.5a**, **2.5b** and **2.5c** were obtained on reaction of ester **2.3a** or acid **2.3b** with *o*-aminothiophenol **2.4a**, *o*-aminophenol **2.4b** or *o*-phenylenediamine **2.4c** (in 40%, 25% and 50 % yields, respectively) (Scheme 2.7). The yields of the desired products

**2.5a,b,c** were higher if acid **2.3b** was used as a condensation agent (an increase with *ca.* +10%).




**2.3a, b** **2.4a-c** **2.5a-c**

**2.3** : **a**: R = $C_2H_5$; **b** : R = H
**2.4, 2.5** :**a** : X = S; **b** : X = O; **c**: X = NH

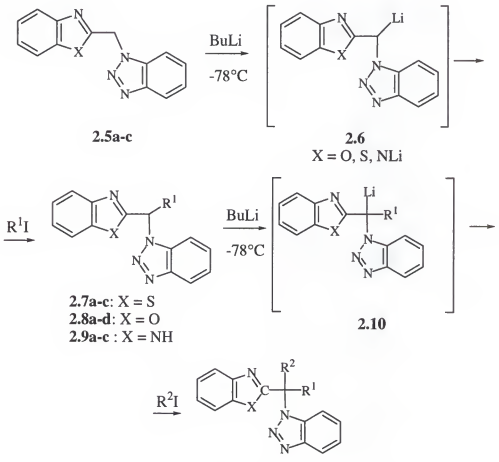
Scheme 2.7

2.2.2. Synthesis of Mono- and Di-substituted 2-(Benzotriazol-1-ylmethyl)benzothiazoles **2.7a-c**, **2.11a-c** , -benzoxazoles **2.8a-d**, **2.12a-d** and -benzimidazoles **2.9a-c**, **2.13a**.

(1,3-Benzazol-2-yl)(benzotriazol-1-yl)-methanes **2.5a**, **2.5b** and **2.5c** readily reacted with one (or two, in the case of **2.5c**) equivalent(s) of *n*-BuLi at -78°C to give the anion **2.6**, which was treated with one equivalent of alkyl iodide. The resulting reaction mixture contained monoalkylated derivatives **2.7a-c**, **2.8a-d, 2.9a-c** as a major component in 30-42% yield (Scheme 2.5) and dialkylated derivatives **2.11a,b**, **2.12a-d, 2.13a** as secondary products in 10-15% yield. If the lithiation was carried out at -100°C, the formation of dialkylated products **2.11a,b**, **2.12a-d, 2.13a** did not occur, and the yields of monoalkylated derivatives **2.7a-c**, **2.8a-d, 2.9a-c** were increased to 85-92%. The mixture could be easily separated by column chromatography (silicagel/ hexane-ether, 1:1) to give pure mono-substituted derivatives **2.7a-c**, **2.8a-d** and **2.9a-c**. The electrophiles used and the yields of the products obtained are presented in Table 2.1. For the benzimidazole derivative **2.5c**, two equivalents of *n*-BuLi were used in the synthesis of **2.9a-c**. As expected, the formation of the dianion **2.6** (X = NLi), followed by reaction

with alkyl iodides, resulted exclusively in **2.7a-c**, **2.8a-d**, **2.9a-c**, the products of alkylation at the carbanion in **2.6**.

Symmetrically and unsymmetrically di-substituted derivatives **2.11a-c**, **2.12a-d** and **2.13a**,**b** were obtained as the major products in 41-55% yield if the mono-substituted compounds **2.7a-c**, **2.8a-d**, **2.9a-c** were treated *in situ* with one (or two, see the previous paragraph) equivalent(s) of *n*-BuLi followed by addition of one equivalent of alkyl iodide (Table 2.2.).




**2.5a-c**

**2.6**
X = O, S, NLi

**2.7a-c**: X = S
**2.8a-d**: X = O
**2.9a-c** : X = NH

**2.10**

**2.11 a-d**: X = S
**2.12 a-e**: X = O
**2.13a ,b**: X = NH

Scheme 2.8

Table 2.1. Preparation of monoalkylated 2-(benzotriazol-1-ylmethyl)benzothiazole **2.7a-c**, -benzoxazole **2.8a-d** and -benzimidazole **2.9a-c** derivatives.

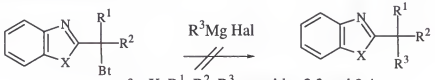
| compd. | X | $R^1$ | mp(°C) | yield (%) | molecular formula | found (required) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **2.7a** | S | $CH_3$ | 97 | 42 | $C_{15}H_{12}N_4S$ | 64.26 (64.10) | 4.31 (4.00) | 19.98 (19.56) |
| **2.7b** | S | $C_4H_9$ | 89 | 43 | $C_{18}H_{18}N_4S$ | 67.05 (67.09) | 5.63 (5.64) | 17.38 (17.39) |
| **2.7c** | S | $C_8H_{17}$ | oil | 43 | $C_{22}H_{26}N_4S$ | 69.81 (69.93) | 6.92 (7.06) | 14.80 (14.85) |
| **2.8a** | O | $CH_3$ | oil | 38 | $C_{15}H_{12}N_4O$ | 68.17 (68.57) | 4.58 (4.40) | 21.20 (21.10) |
| **2.8b** | O | $C_4H_9$ | oil | 30 | $C_{18}H_{18}N_4O$ | 70.57 (70.11) | 5.92 (5.50) | 18.29 (18.13) |
| **2.8c** | O | $C_5H_{11}$ | oil | 38 | $C_{19}H_{20}N_4O$ | 71.23 (71.53) | 6.29 (6.43) | 17.49 (17.10) |
| **2.8d** | O | $C_8H_{17}$ | oil | 37 | $C_{22}H_{26}N_4O$ | 72.90 (73.08) | 7.23 (7.38) | 15.46 (15.47) |
| **2.9a** | N | $CH_3$ | 80 | 50 | $C_{15}H_{12}N_5$ | 68.43 (68.49) | 4.98 (5.35) | 26.60 (26.50) |
| **2.9b** | N | $C_4H_9$ | 152 | 57 | $C_{18}H_{18}N_5$ | 71.03 (70.80) | 5.97 (6.37) | 23.01 (22.69) |
| **2.9c** | N | $C_8H_{17}$ | oil | 62 | $C_{22}H_{26}N_5$ | 73.10 (73.22) | 7.53 (7.45) | 19.37 (19.16) |

Table 2.2. Preparation of dialkylated 2-(benzotriazol-1-ylmethyl)benzothiazole **2.11a-c**, -benzoxazole **2.12a-d** and benzimidazole **2.13a,b** derivatives.

| comp | X | $R^1$ | $R^2$ | mp (°C) | yield (%) | molecular formula | found (required) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **2.11a** | S | $CH_3$ | $CH_3$ | 127 | 35 | $C_{16}H_{14}N_4S$ | 65.28 | 4.79 | 19.03 |
| | | | | | | | (65.51) | (4.80) | (18.94) |
| **2.11b** | S | $C_4H_9$ | $C_4H_9$ | 112 | 35 | $C_{22}H_{26}N_4S$ | 69.81 | 6.92 | 14.80 |
| | | | | | | | (70.16) | (7.13) | (14.79) |
| **2.11c** | S | $CH_3$ | $C_8H_{17}$ | oil | 40 | $C_{23}H_{28}N_4S$ | 70.37 | 7.19 | 14.27 |
| | | | | | | | (70.70) | (7.33) | (14.28) |
| **2.12a** | O | $CH_3$ | $CH_3$ | 126 | 32 | $C_{16}H_{14}N_4O$ | 69.05 | 5.07 | 20.13 |
| | | | | | | | (68.89) | (4.79) | (19.75) |
| **2.12b** | O | $C_4H_9$ | $C_4H_9$ | 104 | 29 | $C_{22}H_{26}N_4O$ | 72.89 | 7.23 | 15.46 |
| | | | | | | | (72.70) | (7.42) | (15.48) |
| **2.12c** | O | $C_5H_{11}$ | $C_5H_{11}$ | 158 | 40 | $C_{24}H_{30}N_4O$ | 73.81 | 7.74 | 14.35 |
| | | | | | | | (74.10) | (7.86) | (14.12) |
| **2.12d** | O | $C_8H_{17}$ | $C_8H_{17}$ | oil | 38 | $C_{30}H_{42}N_4O$ | 75.91 | 8.92 | 11.80 |
| | | | | | | | (75.72) | (9.11) | (11.65) |
| **2.13a** | N | $C_4H_9$ | $C_4H_9$ | 109 | 41 | $C_{22}H_{27}N_5$ | 73.10 | 7.53 | 19.37 |
| | | | | | | | (73.01) | (7.55) | (19.70) |
| **2.13b** | N | $CH_3$ | $C_8H_{17}$ | 106 | 55 | $C_{23}H_{29}N_5$ | 73.57 | 7.78 | 18.65 |
| | | | | | | | (73.13) | (7.80) | (19.07) |

2.2.3. Attempted Displacement of Benzotriazole in compounds **2.7b,c** and **2.11a-c**

Treatment of mono- or di-substituted bis(benzotriazol-1-ylmethyl)-benzazoles with Grignard reagents in toluene according to a procedure previously described [95JOC5638] was expected to result in the displacement of the benzotriazole moiety with formation of the corresponding 2-substituted benzothiazoles, benzoxazoles and benzimidazoles. A series of mono- and di-substituted bis(benzotriazol-1-ylmethyl)-benzothiazoles was treated with $CH_3MgI$, $C_6H_5MgBr$ or $C_6H_5CH_2MgBr$ (Table 2.4), but the reaction did not lead to the expected products. In some cases, the starting material was recovered, whereas more drastic conditions or excess of the Grignard reagent resulted in the products of decomposition (Tables 2.3 and 2.4).




for X, $R^1$, $R^2$, $R^3$ see tables 2.3 and 2.4

Scheme 2.9

The reported successful displacement of the benzotriazolyl group in the Grignard reaction for the series of substituted (1,3-thiazol-2-yl)(benzotriazol-1-yl)methanes [95JOC5638] leads to the conclusion that the benzannelation of the thiazole-, oxazole-, or imidazole ring has a stronger electron-withdrawing effect than could be expected. This effect evidently decreases nucleophilicity of the anions **2.6** and **2.10** that allows them to react only with strong electrophiles such as alkyl iodides. An additional consideration is that according to the suggested mechanism of the benzotriazole displacement in the Grignard reaction, the process is governed by a thermodynamically controlled equilibrium with formation of the benzotriazolyl anion and the corresponding carbocation. The latter would react with the Grignard reagent to yield a product of the benzotriazole displacement. The formation of a carbocation from diazolomethanes **2.7b,c** and **2.11a-c** is probably rendered less thermodynamically favorable because of the effect of benzannelation.

Table 2.3. Reactions of 2-(1-(dimethyl)methylbenzotriazolyl)benzothiazole **2.11a** with $CH_3Mg$ I.

| Ratio **2.11a** : $CH_3MgI$ | Conditions | Results |
|---|---|---|
| **1 : 1.1** | toluene, Δ, 20 h | starting material |
| **1 : 2.1** | toluene, Δ, 20 h | starting material + products of decomposition |
| **1 : 5.0** | toluene, Δ, 20 h | products of decomposition |
| **1 : 10.0** | toluene, Δ, 20 h | products of decomposition |
| **1 : 5.0** | ether, Δ, 20 h | starting material |
| **1 : 5.0** | ether / toluene, Δ, 20 h | starting material |

Table 2.4. Attempted reactions of some mono- and di-substituted 2-(benzotriazol-1-ylmethyl)benzthiazoles with Grignard reagents.

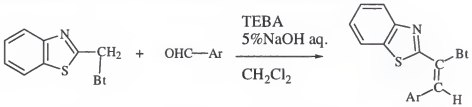
| cmpd. | reagent | ratio | conditions | result |
|---|---|---|---|---|
| **2.7b** | $CH_3MgI$ | 1 : 4 | toluene, 24 h, Δ | products of decomposition |
| **2.11a** | $CH_3MgI$ | 1 : 4 | toluene, 24 h, Δ | products of decomposition |
| **2.11b** | $CH_3MgI$ | 1 : 4 | toluene, 24 h, Δ | products of decomposition |
| **2.11c** | $CH_3MgI$ | 1 : 4 | $Et_2O$ / toluene, 24 h, Δ | starting material |
| **2.11d** | $CH_3MgI$ | 1 : 4 | $Et_2O$, 24 h, Δ | starting material |
| **2.7d** | $C_6H_5MgBr$ | 1 : 4 | $Et_2O$, 24 h, Δ | starting material |
| **2.11b** | $C_6H_5MgBr$ | 1 : 4 | toluene, 24 h, Δ | products of decomposition |
| **2.7c** | $C_6H_5CH_2MgBr$ | 1 : 4 | $Et_2O$ / toluene, 24 h, Δ | starting material |
| **2.11d** | $C_6H_5CH_2MgBr$ | 1 : 4 | $Et_2O$, 24 h, Δ | starting material |
| **2.7b** | $C_6H_5CH_2MgBr$ | 1 : 4 | $Et_2O$, 24 h, Δ | starting material |

2.2.4. Attempted Reactions of the Lithiated 2-Benzotriazolyl Benzothiazole **2.5a** with Various Electrophiles

Lithiation of 2-benzotriazol-1-yl benzothiazole **2.5a** followed by addition of ketones, esters, carbon disulfide, etc. was expected to yield the corresponding substituted 2-benzotriazol-1-yl benzothiazoles, but the reactions failed. The final reaction mixtures contained mostly the starting material and in some cases, products of decomposition. The carbanion **2.6** is not nucleophilic enough to react with the electrophiles selected.

2.2.5. Aldol-type Reaction of 2-Benzotriazolyl Benzothiazole **2.5a** and the Oxidation of 2-(Benzotriazol-1-yl)-2-(benzothiazol-2-yl) Styrene **2.15a.**

We explored the reactivity of the activated methylene group of 2-benzotriazolyl benzothiazole **2.5a** in the aldol-type condensation with aromatic aldehydes **2.14a-c**. The reaction was done under the conditions of phase-transfer catalysis [75TL3519], and afforded the corresponding styryl derivatives **2.15a-c** in 50, 31 and 39% yield, respectively (as single diastereomers, the geometry was unequivocally determined by comparing the NMR data with NMR spectra of similar structures).




**2.5a** **2.14a-c** **a**: Ar = $C_6H_5$- **2.15a-c**

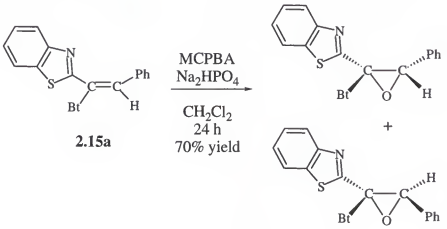
**b**: Ar = *p*-$NO_2C_6H_4$-

Bt = benzotriazol-1-yl

**c**: Ar = 3,4,5-trimethoxyphenyl

Scheme 2.10

The oxidation of the styrene **2.15a** with *m*-chloroperbenzoic acid resulted in the formation of oxirane **2.16a,b** as a mixture of diastereomers. Whereas the $^{1}H$ NMR spectrum of **2.16a,b** does not show an evidence of two isomers and is not characteristic in the structure confirmation (all signals fall in the region of multiplets at 6.80-8.15 ppm), the $^{13}C$ NMR spectrum clearly indicates the presence of two isomers. In addition, the elemental analysis data support the suggested oxirane structure **2.16a,b**.




**2.15a** **2.16a,b**

Scheme 2.11

## 2.3. Conclusions

Our initial objective was not fulfilled, since the benzotriazolyl moiety in mono- or di-alkyl-substituted 2-(1-methylbenzotriazolyl)benzazoles is passive towards the nucleophilic substitution in the Grignard reaction. Nevertheless, we have developed a general and versatile method for the preparation of mono- and di-substituted bis(benzotriazol-1-yl-methyl)-benzazoles.

2-(1-Methylbenzotriazolyl)benzazoles readily form the anion on reaction with *n*-BuLi followed by interaction with alkyl iodides to give the corresponding mono- or di-alkylated derivatives; the reaction with electrophiles other than alkyl iodides (α-bromoacetophenone, benzophenone, ethyl benzoate, carbon sulfide) did not occur.

2-(1-Methylbenzotriazolyl)benzazoles are shown to react with aromatic aldehydes by aldol-type condensation to give β,β-dibenzazolo-substituted styrenes. The novel compounds obtained are expected to possess biological activity (anti-viral, anti-bacterial).

## 2.4 Experimental Part

### General Methods.

Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for $^1H$ (300 MHz) or solvent as the internal standard for $^{13}C$ (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh.

2.4.1 Ethyl (1-Benzotriazolyl)-acetate **2.3a** was prepared by the literature procedure [88CA75308]. Benzotriazole (65.5 mmoles) in benzene (60 ml) was stirred under heat until it dissolved. Ethyl bromoacetate **2a** (17.0 mmoles) was added and the mixture was refluxed 17 hrs. The mixture was cooled to room temperature and extracted with $CHCl_3$ (200 ml), washed with ice-cold NaOH solution (2%, 2x50 ml), and with water (2x100 ml). The extract was dried over $MgSO_4$ and the solvent evaporated to give the product (yield 88%). M.p. 74°C; $^1H$ NMR ($CDCl_3$) δ 1.25 (t, $J$ = 7.1 Hz, 3H), 4.24 (m, 2H), 5.4 (s, 2H), 7.30-7.50 (m, 3H), 8.05 (d, $J$ = 6.3 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 166.2, 145.8, 133.2, 127.7, 127.7, 123.9, 119.9, 109.2, 62.1, 48.9, 13.9; Anal. calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48 ; found: C, 58.58; H, 5.38; N, 20.52.

2.4.2 (1-Benzotriazolyl)-acetic Acid **2.3b**

A mixture of benzotriazole (2.62 g, 22 mmoles) and monochloroacetic acid (1.89 g, 20 mmoles) in dry toluene (20 ml) was refluxed for 18 hours. The mixture was cooled and washed with a concentrated solution of sodium bicarbonate (3 × 20 ml). The aqueous layer was separated, extracted with methylene chloride (2 × 20 ml) and acidified with concentrated hydrochloric acid to pH 4. The precipitate obtained was filtered off, washed with methanol (3 x 5 ml), dried and recrystallized from methanol to give the product (90%), mp 216° (lit. mp 214-216° [15]); $^1$H NMR (DMSO): δ 8.09 (dd, *J* = 8.4 Hz, *J* = 0.9 Hz, 1H), 7.87 (dd, *J* = 8.4 Hz, *J* = 0.9 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 5.69 (s, 2H); $^{13}$C NMR (DMSO): δ 168.8, 145.2, 133.6, 127.5, 124.0, 119.1, 110.8, 48.8.

2.4.3. General Procedure for the Synthesis of 2-(Benzotriazol-1-yl-methyl)-benzazoles **2.5a**, **2.5b** and **2.5c**

2-Aminothiophenol **2.4a**, 2-aminophenol **2.4b** or *o*-phenylenediamine **2.4c** (9.8 mmol) and ethyl (benzotriazol-1-yl)-acetate **2.3** (9.8 mmol) were stirred in PPA (polyphosphoric acid) at 170°C for 4 hrs. The reaction mixture was quenched with ice-cold water, extracted with $CHCl_3$, dried over $MgSO_4$ and the solvent was evaporated to give an oil. The oil was purified by column chromatography (hexane:ether = 5:1) and recrystallized from diethyl ether to give the solid product (yields 40%, 25% and 50%, respectively). In the case of **2.5c** the work-up procedure was different: the reaction mixture was quenched with ice-cold water, neutralized with $NaHCO_3$, then extracted with $CHCl_3$, dried over

$MgSO_4$ and the solvent evaporated to give a solid. The solid was purified by recrystallized from ethanol to give the solid product (yield 50% ).

2-(Benzotriazol-1-yl-methyl)benzothiazole **2.5a** mp 120°C; $^1H$ NMR ($CDCl_3$) δ 6.28 (s, 2H), 7.35-7.63 (m, 5H), 7.8 (d, *J* = 8.1 Hz, 1H), 8.02-8.12 (dd, *J* = 8.1 Hz, *J* = 8.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 165.4, 152.3, 145.2, 134.7, 132.9, 127.8, 126.5, 125.6, 124.3, 122.8, 122.4, 119.3, 110.6, 48.9; Anal. calcd for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04 ; found: C, 63.02; H, 3.76; N, 21.18.

2-(Benzotriazol-1-yl-methyl)benzoxazole **2.5b** mp 118°C; $^1H$ NMR ($CDCl_3$) δ 6.12 (s, 2H), 7.32-7.52 (m, 5H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.71- 7.74 (m, 1H), 8.10 (d, *J* = 8.3, 1H); $^{13}C$ NMR ($CDCl_3$) δ 158.8, 151.0, 146.1, 140.6, 133.0, 128.0, 125.9, 124.8, 124.2, 120.5, 120.2, 110.9, 109.4, 45.4; Anal. calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39 ; found: C, 67.19; H, 3.99; N, 22.31.

2-(Benzotriazol-1-yl-methyl)benzimidazole **2.5c** mp 195°C; $^1H$ NMR (DMSO) d 12.78 (s, H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.58-7.39 (m, 2H), 6.29 (s, 2H); $^{13}C$ NMR (DMSO) δ 148.4, 145.3, 133.1, 127.5, 124.0, 119.1, 110.8, 45.8; Anal. calcd for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45; N, 28.09; found: C, 67.09; H, 4.76; N, 28.18.

2.4.4. General Procedure for the Preparation of Mono- and Dialkylated Symmetrical 2-(Benzotriazol-1-yl- methyl)benzothiazoles **2.7a-c**, **2.11a-b**, and -benzoxazoles **2.8a-d**, **2.12a-d**

*n*-Butyllithium (0.0032 moles) was added to a solution of **2.5a-c** in THF (50 ml) at -78 °C and the solution stirred at this temperature for 2h. The appropriate alkyl iodide (0.0034 moles) was added at -78 °C and the mixture stirred at -78 °C for 4h the at room

temperature overnight. The reaction was quenched with water (30 ml) and the suspension extracted with diethyl ether (3x50 ml). The combined layers were washed with water (2x50 ml), dried over $MgSO_4$ and the solvent removed to give an oil, which was purified by column chromatography (hexane:ether = 1:1). Tables 2.5 and 2.6.

2.4.5. General Procedure for the Preparation of Mono- and Dialkylated Symmetrical 2-(Benzotriazol-1-yl-methyl)benzimidazoles **2.9a-c**, **2.13a**

*n*-Butyllithium (0.0064 moles) was added to a solution of **2.5c** in THF (50 ml) at -100°C and the solution stirred at this temperature for 2h. The appropriate electrophile alkyl iodide (0.0034 moles) was added at -100 °C and the mixture stirred this temperature for an additional 4h, then at room temperature overnight. The reaction was quenched with water (30 ml) and the suspension extracted with diethyl ether (3x50 ml). The combined layers were washed with water (2x50 ml), dried over $MgSO_4$ and the solvent removed to give an oil, which was purified by column chromatography (hexane-ether = 1:2). Tables 2.5 and 2.6.

2.4.6. General Procedure for the Preparation of Dialkylated Unsymmetrical 2-(Benzotriazol-1-yl-methyl)benzothiazoles **2.12c-d** -benzoxazole **2.13e** and -benzimidazole **2.13b**

*n*-Butyllithium (0.0032 moles for **2.5a**,**b** and 0.0064 moles for **2.5c**) was added to a solution of **2.5a-c** in THF (50 ml) at -78 °C and the solution stirred at this temperature for 2 h. The appropriate electrophile alkyl iodide (0.0034 moles) was added at -78 °C and the mixture stirred at this temperature for an additional 4h and at r.t. overnight. *n*-Butyllithium (0.0032 moles for **2.5a**,**b** and 0.0064 moles for **2.5c**) was added to the reaction mixture at -78°C and the solution stirred at this temperature for 2 h. The

appropriate electrophile alkyl iodide (0.0034 moles) was added at -78 °C and the mixture stirred at -78°C for 4h the at room temperature overnight. The reaction was quenched with water (30 ml) and the suspension extracted with diethyl ether (3 x 50 ml). The combined layers were washed with water (2 x 50 ml), dried over $MgSO_4$ and the solvent removed to give an oil, which was purified by column chromatography (hexane-ether = 1:1) (Tables 2.5 and 2.6 a, b).

Table 2.5. $^1H$ NMR data of mono- and dialkylated 2-(benzotriazol-1-ylmethyl) - benzothiazoles -benzoxazoles and -benzimidazoles.

| cmp. | aliphatic<br>H (ppm), J (Hz) | aromatic<br>H (ppm), J (Hz) |
|---|---|---|
| **2.7a** | 2.35 (d, 7.2 Hz, 3H), 6.55 (q, 7.2 Hz, 1H) | 7.30-7.68 (m, 5H), 7.75 (m, 1H), 8.02-8.08 (m, 2H) |
| **2.7b** | 0.88 (t, 7.0 Hz, 3H), 1.29-1.45 (m, 4H), 2.79-2.88 (m, 2H), 6.32-6.37 (m, 1H) | 7.34-7.51 (m, 4H), 7.62 (d, 8.3 Hz, 1H), 7.78-7.81 (m, 1H), 8.04-8.10 (m, 2H) |
| **2.7c** | 0.90 (t, 6.5 Hz, 3H), 1.15-1.50 (m, 12H), 2.70-2.94 (m, 1H), 3.10-3.20 (t, 1H), 6.45-6.52 (m, 1H) | 7.23-7.42 (m, 4H), 7.60-7.75 (m, 2H), 8.50 (m, 2H) |
| **2.8a** | 2.20 (d, 7.1 Hz, 3H), 6.36-6.38 (q, 7.2 Hz, 1H) | 7.46 (d, 8.2 Hz, 1H), 7.62-7.65 (m, 1H), 7.96 (d, 8.2 Hz, 1H) |
| **2.8 b** | 0.87 (t, 7.2 Hz, 3H), 1.20-1.40 (m, 4H), 2.76 (m, 2H), 6.31 (t, 7.9 Hz, 1H) | 7.28-7.47 (m, 5H), 7.64-7.67 (m, 1H), 7.74-7.77 (m, 1H), 8.07-8.10 (m, 1H) |

Table 2.5. continued

| | | |
|---|---|---|
| **2.8c** | 0.83(t, 7.1 Hz, 3H), 1.22-1.45 (m, 6H), 2.75-2.82 (m, 2H), 6.32 (t, 7.8 Hz, 1H) | 7.28-7.47 (m, 5H), 7.64 (d, 8.3 Hz, 1H), 7.74-7.77 (m, 1H), 8.09 (d, 8.3 Hz, 1H) |
| **2.8d** | 0.85 (t, 6.7 Hz, 3H), 1.18-1.45 (m, 12H), 2.75-2.83 (m, 2H), 6.32 (t, 7.9 Hz, 1H) | 7.29-7.47 (m, 5H), 7.66 (d, 8.2 Hz, 1H), 7.74-7.77 (m, 1H), 8.08 (d, 8.2 Hz, 1H) |
| **2.11a** | 2.39 (s, 6H), 7.16-7.36 (m,4H) | 7.44-7.47 (m, 1H), 7.71-7.74 (m, 1H), 8.05-8.10 (m, 2H) |
| **2.11b** | 0.82 (t, 7.1 Hz, 6H), 0.90-1.05 (m,2H), 1.26-1.35 (m,6H), 2.80-3.02 (m, 4H) | 7.04 (d, 7.3 Hz, 1H), 7.15-7.28 (m, 2H), 7.36-7.49 (m, 1H), 7.50-7.54 (m, 1H), 7.75-7.78 (m, 1H), 8.05 (d, 8.2 Hz, 1H), 8.14 (d, 8.4 Hz, 1H) |
| **2.11c** | 0.82 (t, 6.5 Hz, 3H), 0.84-1.50 (m, 12H), 2.38 (s, 3H), 2.74-2.88 (m, 2H) | 7.20-7.47 (m, 5H), 7.70 (d, 7.4 Hz, 1H), 8.04-8.10 (m, 2H) |
| **2.11d** | 0.75-1.40 (m, 22H), 2.78-2.90 (m, 2H), 2.98-3.12 (m, 2H) | 7.00-7.48 (m, 5H), 7.73 (d, 8 Hz, 1H), 8.04 (d, 8.3 Hz, 1H), 8.12 (d, 8.2 Hz, 1H) |
| **2.12a** | 2.40 (s, 6H) | 7.14-7.17 (m, 1H), 7.25-7.42 (m, 5H), 7.80-7.83 (m, 1H), 8.06-8.09 (m, 1H) |
| **2.12b** | 0.83 (t, 7.1 Hz, 6H), 0.95-1.10 (m, 2H), 1.18-1.35 (m, 6H), 2.83-2.94 (m ,4H) | 6.99 (d, 8.6 Hz, 1H), 7.19-7.41 (m, 5H), 7.84 (d, 7.9 Hz, 1H), 8.07 (d, 8.0 Hz, 1H) |
| **2.12c** | 0.79 (t, 6.8 Hz, 6H), 0.95-1.18 (m, 2H), 1.20-1.62 (m, 10H), 2.82-2.92 (m, 4H) | 6.98 (d, 8.2 Hz, 1H), 7.22-7.41 (m, 5H), 7.82-7.86 (m, 1H), 8.07 (d, 8.1 Hz, 1H) |

Table 2.5. continued

| | | |
|---|---|---|
| **2.12d** | 0. 83 (t, 6.8 Hz, 6H), 1.00-1.32 (m, 24 H), 2.82-2.93 (m, 4H) | 6.98 (d, 7.1 Hz, 1H), 7.00-7.42 (m, 5H), 7.83-7.86 (m, 1H), 8.07 (d, 8.1 Hz, 1H) |
| **2.12e** | 0.83 (t, 6.8 Hz, 3H), 1.18-1.87 (m, 12 H), 2.37 (2, 3H), 2.79-2.91 (m, 2H) | 7.09-7.12 (m, 1H), 7.22-7.42 (m, 5H), 7.80-7.83 (m, 1H), 8.05-8.09 (m, 1H) |
| **2.9a** | 2.16 (d, 3H, 7.2 Hz), 6.99-6.42 (m, 1H) | 12.66-12.53 (m, 1H), 7.47 (d, 2H, 8.3 Hz), 7.34 (d, 2H, 8.4 Hz), 7.19-7.02 (m, 4H) |
| **2.9b** | 0.80 (t, 3H, 6.8 Hz), 1.35-1.16 (m, 4H), 2.78-2.73 (m, 2H), 6.42-6.37 (m, 1H) | 12.19-12.13 (m, 1H), 7.85-7.18 (m, 8H) |
| **2.9c** | 0.80 (t, 3H, 6.9 Hz), 1.25-1.11 (m, 12 H), 2.83-2.80 (m, 2H), 6.52-6.47 (dd, 1H, 9 Hz) | 12.85 (s, 1H), 7.80-7.63 (m, 3H), 7.51-7.42 (m, 1H), 7.35-7.30 (m,1H), 7.24-7.17 (m, 3H) |
| **2.13a** | 0.77 (t, 6H, 6.9 Hz), 1.32-1.18 (m, 7H), 1.65 (s, 1H), 2.88-2.79 (m, 2H) | 12.44 (s, 1H), 7.91 (d, 1H, 7.1 Hz), 7.52-7.49 (m, 1H), 7.31-7.19 (m, 3H), 6.99-6.94 (m, 1H), 6.87 (d, 1H, 8.1 Hz), 6.78-6.68 (m, 1H) |
| **2.13 b** | 0.80-0.74 (m, 8H), 1.30-1.17 (m, 16H), 2.89-2.78 (m, 4H) | 12.95 (1H, s), 7.91-7.88 (m, 1H), 7.52-7.49 (m, 1H), 7.29-7.18 (m, 2H), 6.96-6.90 (m, 1H), 6.80-6.66 (m, 3H) |

Table 2.6.a. $^{13}C$ NMR data of mono- and dialkylated 2-(benzotriazol-1-ylmethyl) - benzothiazoles, -benzoxazoles and -benzimidazoles

| cmpd | benzazole | $C_7$ | $C_8$ | benzotriazole | alkyl |
|---|---|---|---|---|---|
| | $C_1$-$C_6$ | | | $C_9$-$C_{14}$ | |
| **2.7a** | 121.7, 124.1, 125.3, 127.5, 132.8, 152.7 | 169.0 | 57.5 | 109.9, 120.0, 123.3, 126.2, 135.5, 146.2 | 19.7 |
| **2.7b** | 121.7, 124.2, 125.6, 127.6, 132.6, 152.5 | 168.6 | 62.2 | 109.9, 120.1, 123.4, 126.2, 135.3, 146.2 | 13.7, 22.0, 28.2, 33.6 |
| **2.7c** | 121.2, 123.6, 125.7, 127.1, 132.2, 152.1 | 168.1 | 61.6 | 109.6, 119.6, 123.0, 125.1, 134.8, 145.8 | 13.5, 22.0, 25.6, 28.4, 28.5, 28.6, 31.2, 33.4 |
| **2.8a** | 120.4, 124.1, 125.8, 127.7, 132.1, 150.8 | 162.2 | 53.1 | 109.7, 110.8, 120.1, 124.7, 140.4,146.3 | 17.7 |
| **2.8b** | 120.5, 124.7, 125.8, 127.8, 132.3, 150.8 | 161.9 | 57.8 | 110.0, 110.9, 120.2, 124.1, 140.5, 146.4 | 13.6, 21.9, 27.9, 31.3 |
| **2.8c** | 120.4, 124.6, 125.7, 127.6, 132.2, 150.7 | 161.8 | 57.7 | 109.9, 110.8, 120.1, 124.0, 140.4, 146.3 | 13.7, 22.1, 25.4, 30.8, 31.5 |
| **2.8d** | 120.4, 124.0, 125.7, 127.6, 132.3, 150.7 | 161.8 | 57.8 | 109.9, 110.9, 120.2, 124.0, 140.4, 146.3 | 13.9, 22.4, 25.7, 28.7, 28.0, 29.0, 31.5, 31.6 |
| **2.11a** | 121.6, 123.6, 125.5, 126.9, 131.9, 152.0 | 173.4 | 65.0 | 111.3, 119.9, 123.4, 126.1, 135.4, 146.8 | 28.6 |
| **2.11b** | 121.7, 123.7, 126.1, 127.1, 132.2, 151.9 | 173.5 | 71.0 | 111.3, 120.1, 123.7, 125.7, 135.5, 140.3 | 13.7, 22.2, 25.0, 36.1 |

Table 2.6.a. continued

| | | | | | | |
|---|---|---|---|---|---|---|
| **2.11c** | 121.5, 123.5, 125.9, 126.8, 132.0, 151.9 | 173.5 | 67.9 | 111.2,119.84, 123.3, 125.4, 135.2, 146.6 | 13.8, 22.2, 23.0, 25.9, 28.7, 28.8, 29.1, 31.4, 39.5 |
| **2.11d** | 121.5,125.4, 125.8, 126.8, 135.2, 151.7 | 173.1 | 70.8 | 111.0, 119.8, 123.4, 126.7, 132.0, 146.5 | 13.5, 13.7, 22.2, 22.3, 24.8, 28.7, 28.8,29.1, 31.4, 35.9, 36.1 |
| **2.12a** | 120.6, 124.8, 127.4, 132.0, 140.0, 151.0 | 162.5 | 61.1 | 110.6, 111.0, 120.2, 123.8, 125.9, 146.9 | 26.8 |
| **2.12b** | 120.2, 124.8, 127.3, 132.4, 140.2, 150.8 | 165.1 | 67.5 | 110.5, 111.1, 120.6, 123.8, 125.8, 146.6 | 13.8, 22.5, 25.2, 34.7 |
| **2.12c** | 120.1, 124.8, 127.4, 132.12, 140.2, 150.8 | 165.1 | 67.5 | 110.5, 111.1, 120.6, 123.8, 125.9, 146.6 | 13.8, 22.3, 22.7, 31.5, 32.7, 34.9 |
| **2.12 d** | 120.2, 124.8, 127.3, 132.2, 140.8, 150.8 | 165.1 | 67.5 | 110.5, 111.1, 120.6, 120.8, 125.8, 146.7 | 14.0, 22.5, 22.6, 22.9, 29.0, 29.1, 29.3, 31.7, 34.9 |
| **2.12 e** | 120.2, 124.8, 127.3, 132.2, 140.3, 150.9 | 165.4 | 64.3 | 110.6, 111.0, 120.6, 123.8, 125.8, 146.8 | 14.0, 22.5, 29.3, 24.1, 29.1, 29.4, 31.7, 38.3 |

Table 2.6.b. $^{13}C$ NMR data of mono- and dialkylated 2-(benzotriazol-1-ylmethyl) -benzothiazoles, -benzoxazoles and -benzimidazoles

| cmpd | aromatic | C7 | C8 | alkyl |
|---|---|---|---|---|
| **2.9a** | 145.6, 132.0, 127.8, 124.5, 118.9, 110.2 | 151.2 | 54.5 | 18.9 |
| **2.9b** | 145.6, 132.5, 127.9, 124.5, 119.1, 110.3 | 150.8 | 59.0 | 33.1, 28.1, 22.0, 13.7 |
| **2.9c** | 145.5, 142.4, 134.5, 132.4, 127.7, 124.4, 123.3, 122.2, 119.2, 118.9, 111.5, 110.3 | 150.8 | 58.9 | 32.9, 31.5, 29.0, 28.8, 28.7, 25.8, 22.4, 13.8 |
| **2.13a** | 145.2, 142.4, 134.9, 131.8, 127.1, 124.3, 123.3, 122.0, 120.0, 117.6, 111.5, 111.0 | 154.6 | 58.5 | 35.4, 25.1, 22.6, 13.9 |
| **2.13b** | 145.0, 142.2, 134.8, 131.6, 126.8, 124.0, 123.1, 121.8, 119.7, 117.4, 111.2, 110.9 | 154.4 | 68.5 | 35.4, 25.1, 22.6, 13.9 |

2.4.6. General Procedure for the Preparation of 2-(Benzotriazol-1-yl)-2-(benzothiazol-2-yl)styrenes **2.15a-c**

The mixture of 2-(1-methylbenzotriazol-1-yl)benzothiazole (10 mmol), 3,4,5-trimethoxy benzaldehyde (10 mmol), NaOH (3 ml, solution 50%) and a spatula tip of TEBA (triethylbenzylammonium chloride) were stirred in 50 ml $CH_2Cl_2$ at room temperature over night. The reaction mixture was extracted with $CH_2Cl_2$, washed with AcOH 10%, then with water and finally evaporated to give an oil. After crystallization from ethyl ether the desired product was obtained.

1-(Benzothiazol-2-yl)-1-(benzotriazol-1-yl)-2-phenylethene **2.15a**

M.p. 154°C; $^1$H NMR ($CDCl_3$) δ 8.28 (s, 1H), 8.21-8.18 (m, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.49-7.08 (m, 8H), 6.80 (d, *J* = 7.6 Hz, 1H); $^{13}$C NMR δ 164.9, 153.6, 145.7, 135.2, 133.1, 132.9, 131.7, 130.1, 129.6, 128.7, 128.4, 127.0, 126.6, 125.6, 125.6, 124.4, 123.3, 121.5, 120.1, 110.0; Anal. calcd for $C_{21}H_{14}N_4S$: C, 71.17; H, 3.98; N, 15.81; found: C, 71.20; H, 3.73; N, 15.76.

1-(Benzothiazol-2-yl)-1-(benzotriazol-1-yl)-2-(4-nitrophenyl)ethene **2.15b**

M.p. 210°C; $^1$H NMR ($CDCl_3$) δ 8.30 (s, 1H), 8.23-8.20 (m, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.57-7.40 (m, 4H), 7.27-7.20 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR δ 163.7, 153.7, 147.8, 145.7, 138.2, 135.6, 132.9, 130.4, 130.1, 129.8, 129.0, 127.1, 126.3, 125.0, 123.9, 123.8, 121.8, 120.6, 109.8; Anal. calcd for $C_{21}H_{13}N_5SO_2$: C, 63.15; H, 3.28; N, 17.53; Found: C, 63.00; H, 3.12; N, 17.42.

1-(Benzothiazol-2-yl)-1-(benzotriazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethene **2.15c**

M.p. 170°C; $^1$H NMR ($CDCl_3$) δ 8.21-8.18 (m, 2H), 7.69-7.66 (m, 6H), 5.65 (s, 2H), 3.53 (s, 3H), 3.20 (s, 6H); $^{13}$C NMR δ 159.9, 153.1, 151.0, 145.8, 136.5, 128.7, 126.5, 125.9, 125.0, 124.5, 120.5, 110.5, 110.1, 107.3, 60.8, 55.7; Anal. calcd for $C_{24}H_{24}N_4SO_3$: C, 64.27; H, 5.39; N, 12.49; Found: C, 64.01; H, 5.30; N, 12.32.

2.4.7. Oxidation of 2-(Benzotriazol-1-yl)-2-(benzothiazol-2-yl) Styrene **2.15a**

2-(Benzotriazol-yl)- 2-(benzothiazol-2-yl) styrene (0.6 g, 1.69 mmol), MCPBA (*m*-chloroperbenzoic acid) (1.17 g, 3.4 mmol) and $Na_2HPO_4$ (0.2 g, 4.23 mmol) were stirred at r.t. in $CH_2Cl_2$ for 3 days. The reaction mixture was filtered, the filtrate washed

with 10% solution $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give the product as a solid (yield 20%).

1-(Benzothiazol-2-yl)-1-(benzotriazol-1-yl)-2-phenylethene Oxirane **2.16 a,b**

M.p. 145°C; $^1H$ NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.20-8.18 (m, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 6.1 Hz, 1H), 7.57-7.40 (m, 4H), 7.51-7.33 (m, 4H), 7.26-7.08 (m, 1H), 6.80 (d, *J* = 6.1 Hz, 2H); $^{13}C$ NMR δ 164.9, 161.6, 153.6, 145.7, 135.1, 134.9, 134.3, 133.2, 132.9, 131.7, 130.1, 129.5, 128.7, 127.7, 126.9, 126.9, 126.6, 125.6, 124.5, 123.3, 121.5, 120.1, 110.0; Anal. calcd for $C_{21}H_{14}N_4SO$: C, 68.09; H, 3.81; N, 15.12; found: C, 67.99; H, 4.07; N, 14.82.

CHAPTER 3

# SELECTIVE REACTIVITY OF $SP^2$ AND $SP^3$-CARBANIONS OF 1-SUBSTITUTED 1,2,4-TRIAZOLES

## 3.1 Introduction

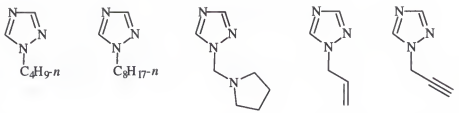
Many heteroaromatic ring systems which contain electronegative heteroatoms (N, S, O) are long known to undergo facile C-metallations of two distinct types: (i) at a $sp^2$-hybridized carbon atom adjacent to a heteroatom [55JOC225, 79JCS(P1), 93AHC208, 97CR721] and (ii) at an $\alpha$-$sp^3$-hybridized carbon atom of C-alkyl substituents. In recent years, considerable attention has been paid to a third type of C- metallation, *i.e.* that at the $\alpha$-position of *N*-alkyl groups [95JOC1244].

The aforementioned considerations apply to substituted 1*H*-1,2,4-triazoles. The similar properties of C-alkyl substituents on triazoles to those on benzene are widely recognized [85MI1]. By contrast, until recently, the reactivity of *N*-substituents on triazoles, as with *N*-substituents on heterocycles in general, has been much less investigated [85MI1]. Most studies of the lithiation of *N*-substituted triazoles have been in connection with the protection of the 1-NH during C-lithiation at C-5 and subsequent reaction with electrophiles [93AHC208]. 5-Metallated 1*N*-protected 1*H*-1,2,4-triazoles were used as nucleophiles in reactions with various electrophiles to give the corresponding 1,5-disubstituted triazoles, which were further deprotected to 3- (≡5)-substituted derivatives [82LA1387, 90T641]. In the course of such work, rearrangements between 5-C and 3-C isomers have appeared to occur readily: thus, lithiated 1-(pyrrolidinomethyl)-1,2,4-triazole reacted with electrophiles to afford the 1,5-disubstituted product, which

underwent isomerization to produce an equilibrium mixture in which the less sterically hindered 1,3-disubstituted derivative prevailed [90T641]. However, in fact such rearrangements involve movement of the *N*-substituent from 1-*N* to 2-*N*, while the C-substituent remains attached to the same ring carbon [90T641]; for similar behavior see ref [97TA1491]. To our knowledge, substitution at the exocyclic *N*-methylene group of a 1*H*-1,2,4-triazole was previously reported only for 1-benzyl-1*H*-1,2,4-triazole, and only when benzyl halides were used as an electrophile [85S302, 90JHC673]. Substitution at an exocyclic *N*-methyne group in 1-(α-ethoxyallyl)- and 1-(α-ethoxypropynyl)- [97JOC706, 97JOC715] 1*H*-1,2,4-triazole has been developed as an important synthetic procedure in our group.

There is much practical interest in triazole derivatives [61CR87, 84MI1, 96MI1], but mechanistic aspects have been relatively neglected. We now present a comparative study of the C-metallation and subsequent treatment with electrophiles of 1-alkyl-, 1-allyl- and 1-propargyl-1*H*-1,2,4-triazoles, to evaluate their substitution patterns and to help to expand the functionalization routes in this class.

The 1*H*-1,2,4-triazole derivatives **3.1-3.5** used as substrates for the present study are known compounds and were prepared by previously described methods. 1-*n*-Butyl- (**3.1**) and 1-*n*-octyl-1,2,4-triazole (**3.2**) were made by direct alkylation of 1*H*-1,2,4-triazole with haloalkanes [86CA22645]. 1-(1-Pyrrolidinomethyl)-1*H*-1,2,4-triazole (**3.3**) was obtained by a Mannich-type reaction of 1,2,4-triazole with formaldehyde and pyrrolidine [90T641]. 1-Allyl-1,2,4-triazole (**3.4**) was prepared by reacting 1*H*-1,2,4-triazole with allyl bromide [80JOM141], while 1-propargyl-1*H*-1,2,4-triazole (**3.5**) [94H1367] was obtained by adapting the method described for the preparation of 1-propargylbenzotriazole [92LA843].



**3.1** **3.2** **3.3** **3.4** **3.5**

Scheme 3.1

These substrates were lithiated and subsequently reacted with $D_2O$ (or $H_2O$), alkyl iodides and benzophenone, by some or all of five standardized procedures of lithiation/treatment with electrophile which are classified below as (A) - (E). These procedures were aimed at the elucidation of the regioselectivity of the first and subsequent lithiations, along with the determination of the regioselectivity of the ambident carbanions in their reactions with electrophiles. A series of similar experiments involving 1-allyl-1,2,4-triazole (**3.4**) and 1-propargyl-1*H*-1,2,4-triazole (**3.5**), which were later carried out in our group and are briefly described for comparison purposes.

(A) For compounds **3.1**-**3.5**: reaction with 1 equiv of *n*-BuLi, and subsequently with 1 equiv of electrophile. These experiments established that, for 1-alkyl- and 1-allyl-1*H*-1,2,4-triazoles, the carbanion was formed at the 5-C, the position already reported as the most reactive lithiation site [96MI1], while for 1-propargyl-1*H*-1,2,4-triazole the first lithiation occurred at the alkyne hydrogen.

(B) For compounds **3.2**, **3.4** and **3.5**: two consecutive sequences of reactions, each consisting of treatment with 1 equiv of *n*-BuLi, and subsequently 1 equiv of electrophile. These experiments showed the orientation of the second lithiation and provided information on the relative reactivities of the centers.

(C) For compounds **3.4** and **3.5**: reaction with 2 equiv of *n*-BuLi, and subsequent treatment with 2 equiv of electrophile.

(D) For compounds **3.4** and **3.5**: reaction with 2 equiv of *n*-BuLi and then with 1 equiv of an electrophile, followed by quenching with water.

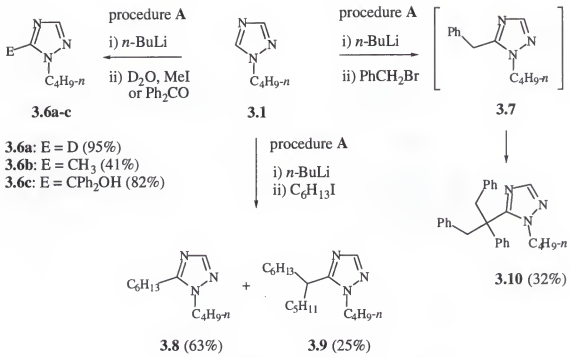
(E) For compound **3.5**: reaction with 3 equiv of *n*-BuLi, and then 1 equiv of an electrophile (*i.e.* benzophenone), followed by quenching with water.

## 3.2 Results and Discussion

### 1-Alkyl-1*H*-1,2,4-triazoles **1** and **2**.

Previous studies of the lithiation of 1-alkyl-substituted 1*H*-1,2,4-triazoles are related to the functionalization of the triazole ring [96MI1]. Various alkyl substituents were used as protective groups for the 1-NH of 1*H*-1,2,4-triazole to induce lithiation at C-5. Previous examples of substitution at the exocyclic carbon of the *N*-substituent are uncommon [93AHC208].

Treatment of 1-*n*-butyl-1,2,4-triazole (**3.1**) with *n*-BuLi and subsequently with $D_2O$, iodomethane or benzophenone gave exclusively the corresponding 5-substituted derivatives **3.6a-c**, as expected. The reaction of lithiated **3.1** with 1 equiv of benzyl bromide followed an unexpected route, to give compound **3.10** with a conversion of 32% (conversion of benzyl bromide 100%), while 68% of the starting material was recovered (Scheme 3.2). The monoalkylated derivative **3.7** initially formed was not detected in the crude reaction mixture. The product **3.10** evidently originated from the double deprotonation of lithiated **3.9**. The reaction of lithiated **3.1** with 1 equiv of 1-iodohexane gave a mixture of the 5-monoalkylated derivative **3.8** and the dialkylated product **3.9**, in a ratio of 3:1.




**3.6a-c**

**3.6a**: E = D (95%)
**3.6b**: E = $CH_3$ (41%)
**3.6c**: E = $CPh_2OH$ (82%)

**3.1**

**3.7**

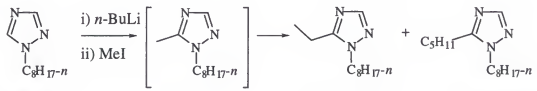
**3.10** (32%)

**3.8** (63%)

**3.9** (25%)

Scheme 3.2

When 1-*n*-octyl-1*H*-1,2,4-triazole (**3.2**) was reacted with iodomethane under conditions (B), products **3.12** and **3.13** were obtained in a ratio of 3:2 (Scheme 3.3 reports the experimental yields, as separated by column chromatography). A second lithiation obviously occurred at the 5-$CH_3$ of the intermediate **3.11**. Compound **3.13** was probably formed *via* the reaction with 1-iodobutane, which results from the exchange between *n*-BuLi and iodomethane.




**3.2** **3.11** **3.12** (32%) **3.11** (40%)

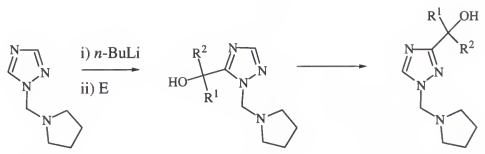
Scheme 3.3

The structures of products **3.6-3.13** were confirmed by $^{1}H$ and $^{13}C$ NMR assignments: the $^{1}H$ NMR spectra evidenced the presence of a hydrogen atom at 3-C of the triazole ring (at *ca.* 8 ppm), while the $^{13}C$ NMR spectra revealed the signals for the corresponding carbon atoms (3-C=N at *ca.* 125 ppm). The substitution at 5-C was confirmed by the disappearance of the signal characteristic for the 5-CH proton. Moreover, the Attached Proton Test (APT) showed the corresponding carbon atoms to be quaternary.

1-(1-Pyrrolidinomethyl)-1*H*-1,2,4-triazole (**3. 3**).

The pyrrolidinomethyl synthon is utilized as a protective group for the 1-NH of 1*H*-1,2,4-triazoles when synthetic purposes require functionalization of a 1-*H*-1,2,4-triazole *via* ring lithiation [90T641]. In compounds of type **3** lithiation proceeds at 5-C, but the 5-substituted products are in mobile equilibrium with their 3-substituted regioisomers, because of the easy rearrangement of the pyrrolidinomethyl substituent to the adjacent N-atom *via* cationotropy [90T641, 97TA1491].

Compound **3.3** was reacted in conditions (A) with benzaldehyde to give the expected product as a mixture of its 3- and 5-regioisomers **3.14a** and **3.14b**, respectively, in a ratio of 1:1 (yield 76%). When reacted with benzophenone in the same conditions (A) a mixture of regioisomers **3.15a** and **3.15b** in a ratio of 1:2 was obtained (yield 80%). The ratio of the two regioisomers in each pair was determined by NMR by using the two distinct singlets at *ca.* 8 ppm, characteristic for the two ring hydrogen atoms.




**3.3** **3.14a** **3.15a** **3.14b** **3.15b**

Scheme 3.4

As expected, monolithiation of 1-alkyl-1*H*-1,2,4-triazoles **3.1-3.3** occurred at 5-C in the ring, and 5-substituted derivatives were generally formed in the reaction with alkyl halides, deuterium oxide and benzophenone (Schemes 3.2 and 3.4). Rearrangement of the 5-C to the 3-C isomer occurred only in the case of the pyrrolidinomethyl derivative **3.3**, where cationotropy is expected [90T641, 97TA1491]. Similar isomerizations were neither expected nor found for 1-butyl- (**3.1**), 1-octyl- (**3.2**), 1-allyl- (**3.4**) and 1-propargyl-1*H*-1,2,4-triazole (**3.5**). Subsequent lithiation in the 5-alkyl-1-*n*-octyl-1*H*-1,2,4-triazoles derived from compound **2** was directed to the α-exocyclic CH of the 5-substituent (Scheme 3.3). During the monolithiation/reaction of compounds **3.1** and **3.2** with electrophile, the product was sometimes more reactive than the starting material and underwent a second or even a third lithiation at the 5-methylene group, as shown for benzyl bromide and 1-iodooctane (Schemes 3.2 and 3.3). No C-metallation at the exocyclic *N*-methylene group was found for any of the 1-alkylsubstituted 1*H*-1,2,4-triazoles **3.1-3.3**.

1-Allyl-1*H*-1,2,4-triazole (**3.4**) under conditions (A) follows the general rule of initial lithiation at the 5-position and thus of substitution at 5-C in the monolithiation/reaction with electrophile. Under conditions (B), the second lithiation occurs either in the methyl group introduced into the 5-position or at the exocyclic N-$CH_2$ However, under conditions (C) and (D) the second lithiation now occurs readily at the

exocyclic N-C<u>H</u>$_2$ leading to the formation of an ambident dianion which can react with an electrophile at one or two of the three alternative positions: the α-exocyclic C<u>H</u> in position 5, and the α- and γ-exocyclic C<u>H</u> at the 1-*N* substituent.

1-Propargyl-1*H*-1,2,4-triazole (**3.5**), unlike the other *N*-substituted 1*H*-1,2,4-triazoles studied, initially undergoes lithiation at the γ-exocyclic position, evidently as a result of the high acidity of this proton, whereas the second lithiation occurs at the 5-C of the ring.

## 3.3 Experimental Part

**General.** Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for $^1H$ (300 MHz) or solvent as the internal standard for $^{13}C$ (75 MHz), unless otherwise stated. The abbreviations for the multiplicity of the proton signals are as follows: q for quartet, qv for quintet, sx for sextet and h for heptet. GC-MS spectra were performed on a HP5890 series II GC HP 5972 MSD instrument, equipped with a HP5 30 m column. Retention times ($R_T$) are given in minutes. THF was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. 1-*n*-Butyl-1*H*-1,2,4-triazole (**3.1**) was prepared by a procedure previously described [96MI1]. Benzophenone, iodomethane, 1-iodohexane, 1-iodooctane, benzyl bromide and phenyl isocyanate were purchased from Fisher.

**Note.** In some cases, compounds were isolated as mixtures and, if they were not considered to present synthetical interest, further purification was not performed.

Assignments were made on the basis of $^{1}H$ and $^{13}C$ NMR spectra and GC-MS results, which are presented in the supplementary material.

1-Octyl-1*H*-1,2,4-triazole (**3**,**2**).

Finely ground 1*H*-1,2,4-triazole (10 mmol), NaOH (40 mmol) and DMF (10 mL) were stirred for 5 min, then iodooctane (2.4 g, 10 mmol) was added. After 15 min, the reaction mixture was poured in water (50 mL), extracted with chloroform (3 × 50 mL), dried ($MgSO_4$) and the solvent evaporated under vacuum. The product was purified by flash vacuum chromatography on silica gel, using successively hexane and diethyl ether as eluent; yellow oil [86CA22645], 1.3 g (70%). $^{1}H$ NMR δ 8.06 (s, 1H), 7.93 (s, 1H), 4.16 (t, $J$ = 6.9 Hz, 2H), 1.89 (qv, $J$ = 6.9 Hz, 2H), 1.32-1.20 (m, 10H), 0.87 (t, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR δ 13.7, 22.2, 26.1, 28.6, 28.7, 29.4, 31.3, 49.3, 142.4, 151.4.

1-(1-Pyrrolidinomethyl)-1*H*-1,2,4-triazole (**3**,**3**).

1*H*-1,2,4-Triazole (7.81 g, 0.11 mol), pyrrolidine (8.5 g, 0.12 mol) and a solution of formaldehyde in water (37% w/w, 10 mL, 0.12 mol) were dissolved in ethanol (50 mL). The mixture was refluxed for 4 h, then the solvent was removed under vacuum. The resulting residue was diluted with water (50 mL), extracted with chloroform (3 x 25 mL) and dried ($Na_2SO_4$). The extract was concentrated, and the residue was subjected to distillation (bp 100 °C/1.2 mm Hg) to give a colorless oil [82LA1387], 14.4 g (86%); $^{1}H$ NMR δ 8.15 (s, 1H), 7.95 (s, 1H), 5.14 (s, 2H), 2.74-2.69 (m, 4H), 1.79-1.74 (m, 4H); $^{13}C$ NMR δ 23.6 (2C), 49.5 (2C), 66.3, 143.3, 151.3.

1-Allyl-1*H*-1,2,4-triazole (**3**,**4**).

1*H*-1,2,4-Triazole (17.25 g, 0.25 mol) was added to a solution prepared from sodium metal (5.75 g, 0.25 mol) in absolute EtOH (90 mL). After complete dissolution, the reaction mixture was heated at 40 °C for 0.5 h, when allyl bromide (22.7 mL, 0.26 mol) was added in one portion. The reaction mixture was stirred at 75 °C for 12 h, then cooled to rt, filtered and concentrated under vacuum to a semicrystalline residue which was taken in chloroform (100 mL). The organic extract was filtered, concentrated under vacuum, and the residue was distilled (bp 94-95 °C/12 mm Hg) to yield a colorless liquid [80JOM141], 16.35 g (60%); $^1$H NMR δ 8.12 (s, 1H), 7.96 (s, 1H), 6.01 (ddt, $J$ = 6.0 Hz, $J$ = 10.2 Hz, $J$ = 17.1 Hz, 1H), 5.35 (d, $J_{cis}$ = 10.2 Hz, 1H), 5.28 (d, $J_{trans}$ = 17.1 Hz, 1H), 4.81 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR δ 51.8, 119.6, 131.0, 142.5, 151.8.

1-Propargyl-1*H*-1,2,4-triazole (**3**,**5**).

1*H*-1,2,4-Triazole (15 g, 0.217 mol) in absolute EtOH (150 mL) was cooled at 0 °C in an ice bath, and a solution of NaOH (8.70 g, 0.217 mol, in 15 mL water) was added. When the sodium triazolate precipitated, propargyl bromide (25 mL, as 80% w/w in toluene, 0.224 mol) was added dropwise at 0 °C (about 1 h). The reaction mixture was allowed to gradually reach rt and was kept under stirring for an additional 48 h, when the final pH was below 8.5. Water (100 mL) was added until the solution was clear, and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 150 mL). The organic solution was washed with water (50 mL, to neutrality), dried ($MgSO_4$) and concentrated under vacuum to give crude product as an orange liquid (19 g), which was purified by distillation (bp 53-

55 °C/0.8-1 mm Hg). The compound solidified upon standing to give yellow crystals, mp 44-6°C (lit. [94H1367] 45-6 °C); 13.86 g (58%). $^1$H NMR δ 8.31 (s, 1H), 7.97 (s, 1H), 5.00 (d, *J* = 2.5 Hz, 2H), 2.64 (t, *J* = 2.5 Hz, 1H), $^{13}$C NMR δ 39.2, 74.9, 75.7, 142.6, 152.1.

Functionalized 1-Alkyl-1*H*-1,2,4-triazoles.

Conditions (A): synthesis of compounds **3.6a-c**, **3.7**, **3.8**, **3.10**, **3.14a,b** and **3.15a,b**.

The appropriate 1-alkyl-1*H*-1,2,4-triazole (0.34 M in THF) was treated at -78 °C with an equimolar amount of *n*-BuLi (1.6 M solution in hexane) to give a yellow suspension. After 15 min, the theoretical amount of electrophile (20% in THF) was added and the reaction was allowed to warm to rt. The reaction was quenched with a saturated solution of $NH_4Cl$ (50 mL) and extracted with $CH_2Cl_2$ (50 mL). The organic layer was dried ($MgSO_4$), the solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography.

1-Butyl-5-*D*-1*H*-1,2,4-triazole (**3.6a**).

Obtained as an oil by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and quenching the reaction mixture with $D_2O$ at rt (95%); $^1$H NMR δ 7.93 (s, 1H), 4.18 (t, *J* = 7.2 Hz, 2H), 1.90-1.83 (m, 2H), 1.33 (sx, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR δ, 13.2, 19.4, 1.5, 49.2, 141.9, 142.3, 151.6. HRMS (POS FAB NBA) 126.1060 (M+1). Calcd for $C_6H_{10}N_3D$ 126.1016.

1-Butyl-5-methyl-1*H*-1,2,4-triazole (**3 .6b**).

Obtained as an oil by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and electrophilic substitution with iodomethane (41%); $^1$H NMR δ 7.77 (s, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.82 (qv, *J* = 7.8 Hz, 2H), 1.38-1.30 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR δ 11.3, 13.0, 19.2, 31.2, 47.5, 149.6, 150.9. HRMS (EI) 139.1111. Calcd for $C_7H_{13}N_3$ 139.1109.

(1-Butyl-1*H*-1,2,4-triazol-5-yl)(diphenyl)methanol (**3 .6c**).

Obtained exclusively as the 5-isomer by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and electrophilic substitution with benzophenone; mp 120-2 °C (82%); $^1$H NMR δ 7.68-7.66 (m, 1H), 7.35-7.33 (m, 6H), 7.26-7.22 (m, 4H), 4.45-4.34 (m, 1H), 3.87 (t, *J* = 7.8 Hz, 2H), 1.44-1.34 (m, 2H), 1.12-1.00 (m, 2H), 0.72 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR δ 13.4, 19.6, 31.1, 49.9, 78.1, 127.4, 128.0, 128.1, 143.4, 148.9, 158.0. Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.49; H, 7.06; N, 13.78.

1-Butyl-5-hexyl-1*H*-1,2,4-triazole (**3 .7**).

Obtained as an oil by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and electrophilic substitution with iodohexane (73%); $^1$H NMR δ 7.79 (s, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.87-1.72 (m, 4H), 1.41-1.23 (m, 8H), 0.98-0.84 (m, 6H); $^{13}$C NMR δ 13.1, 13.5, 19.4, 22.0, 25.4, 27.2, 28.5, 31.0, 31.5, 47.4, 149.8, 154.8. Anal. Calcd for $C_{12}H_{23}N_3$: C, 68.85; H, 11.07; N, 20.07. Found: C, 68.48; H, 11.67; N, 20.09.

1-Butyl-5-(6-dodecyl)-1*H*-1,2,4-triazole (**3 .9**).

Obtained as an oil by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and electrophilic substitution with iodohexane (10%); $^1$H NMR δ 7.83 (s, 1H), 4.06 (t, *J* = 7.5 Hz, 2H),

2.74-2.80 (m, 1H), 1.63-1.88 (m, 6H), 1.04-1.40 (m, 16H), 0.96 (t, $J$ = 7.3 Hz, 3H), 0.83-0.85 (m, 6H); $^{13}$C NMR δ 13.6, 13.9, 14.0, 19.8, 22.4, 22.5, 27.1, 27.4, 29.2, 31.6, 31.7 (2C), 32.1, 34.8, 36.9, 150.4, 158.7. HRMS (EI) 293.2829. Calcd for $C_{18}H_{35}N_3$ 293.2830.

5-(1-Benzyl-1,2-diphenylethyl)-1-butyl-1*H*-1,2,4-triazole (**3.10**).

Obtained by lithiation of 1-butyl-1*H*-1,2,4-triazole (**1**) and electrophilic substitution with benzyl bromide; white solid, mp 89-90 °C (32%); $^1$H NMR δ 7.85 (s, 1H), 7.31-7.03 (m, 11H) 6.65 (d, $J$ = 8.0 Hz, 4H), 3.57-3.46 (m, 4H), 3.35-3.30 (m, 2H), 1.49-1.39 (m, 2H), 0.95-0.88 (m, 2H), 0.61 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR δ 13.2, 19.7, 30.2, 43.3, 49.2 (2C), 65.9, 126.5 (2C), 127.1, 127.5, 127.7 (4C), 128.4 (2C), 130.6 (4C), 136.4 (2C), 142.9, 149.3 (2C), 159.0. Anal. Calcd for $C_{27}H_{29}N_3$: C, 81.99; H, 7.39; N, 10.62. Found: C, 81.81; H, 7.50; N, 10.59.

Phenyl[(1-pyrrolidinomethyl)-*1H*-1,2,4-triazol-3(5)-yl]methanol (**3.14a,b**).

Obtained as a mixture of 3- and 5-isomers in a 1:2 ratio by lithiation of 1-(1-pyrrolidinomethyl)-1*H*-1,2,4-triazole (**3.3**) and electrophilic substitution with benzaldehyde, white solid, mp 86-87 °C (lit. [90T641] 87 °C) (76%); $^1$H NMR δ 8.02 (s, 1H, **3.14a**), 7.80 (s, 1H, **3.14b**), 7.48 (d, $J$=7.2 Hz, 2H, **3.14a,b**), 7.38-7.24 (m, 10H, **3.14a,b**), 6.10 (s, 1H, **3.14b**), 5.92 (s, 1H, **3.14a**), 5.04 (s, 2H, **3.14a**), 4.61 (d, $J$ =12.0 Hz, 1H, **3.14b**), 4.47 (d, $J$ =12.0 Hz, 1H, **3.14b**), 2.68-2.52 (m, 8H, **3.14a,b**), 1.85-1.72 (m, 8H, **3.14a,b**); $^{13}$C NMR δ 23.3 (2C, **3.14b**), 23.7 (2C, **3.14a**), 49.8 (2C, **3.14a**), 50.8 (2C, **3.14b**), 66.6 (**3.14a**), 68.00 (**3.14b**), 68.02 (**3.14b**), 70.4 (**3.14a**), 125.5 (2C, **3.14b**), 126.5 (2C, **3.14a**), 127.6 (**3.14a**), 127.8

(**3.14b**), 128.2 (2C, **3.14a**), 128.4 3 (2C, **3.14b**), 139.9 (**3.14b**), 141.7 (**3.14b**), 144.0 (**3.14a**), 149.3 (**3.14a**), 157.4 (**3.14b**), 165.5 (**3.14a**).

Diphenyl[(1-pyrrolidinomethyl)-*1H*-1,2,4-triazol-3(5)-yl]methanol (**3.15a,b**).

Obtained as a mixture of 3- and 5-isomers in a ratio of 2:1 by lithiation of 1-(1-pyrrolidinomethyl)-1*H*-1,2,4-triazole (**3.3**) and electrophilic substitution with benzophenone; white solid, mp 121-122 °C (lit. [97TA1491] 121-2 °C) (80%), $^1$H NMR δ 8.71 (brs, 1H, **3.15a**), 8.06 (s, 1H, **3.15b**), 7.77 (s, 1H, **3.15a**), 7.45-7.24 (m, 20H, **3.15a+3.15b**), 5.07 (s, 2H, **3.15b**), 4.57 (br. s, 1H, **3.15b**), 4.44 (s, 2H, **3.15a**), 2.71-2.66 (m, 4H, **3.15b**), 2.50-2.48 (m, 4H, **3.15a**), 1.85-1.79 (m, 4H, **3.15a**), 1.79-1.71 (m, 4H, **3.15b**); $^{13}$C NMR δ 23.3 (2C, **3.15b**), 23.9 (2C, **3.15a**), 49.7 (2C, **3.15b**), 50.9 (2C, **3.15a**), 66.7 (**3.15b**), 69.0 (**3.15a**), 76.3 (**3.15b**), 77.8 (**3.15a**), 126.9 (2C, **3.15b**), 127.2 (4C, **3.15a**), 127.4 (4C, **3.15b**), 127.5 (4C, **3.15a**), 127.7 (4C, **3.15b**), 128.0 (2C, **3.15a**), 143.7 (2C, **3.15b**), 143.8 (2C, **3.15a**), 145.3 (**3.15b**), 148.8 (**3.15a**), 160.5 (**3.15b**), 167.8 (**3.15a**).

Conditions (**B**): synthesis of compounds **3.12** and **3.13**.

The appropriate 1-alkyl-1*H*-1,2,4-triazole (0.34 M in THF) was lithiated at -78 °C with the equimolar amount of *n*-BuLi (1.6 M solution in hexane) to give a yellow suspension. After 15 min, the theoretical amount of electrophile (20% in THF) was added dropwise and the reaction was kept at -78 °C for 2 h. The reaction mixture was again lithiated with the equimolar amount of *n*-BuLi (1.6 M solution in hexane) and, after 15 min, the theoretical amount of electrophile (20% in THF) was added. The reaction was allowed to warm to rt, was quenched with a saturated solution of $NH_4Cl$ (50 ml) and

extracted with $CH_2Cl_2$ (50 ml). The organic solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography.

5-Ethyl-1-octyl-1,2,4-triazole (**3.12**).

Obtained by lithiation of 1-octyl-1*H*-1,2,4-triazole (**3.2**) and electrophilic substitution with iodomethane. The crude product obtained as an oil was separated by chromatography on silica gel, using hexane-ether (1:2) as eluent to give 1-octyl-5-pentyl-1,2,4-triazole (**3.13**) as the first fraction and 1-octyl-5-ethyl-1,2,4-triazole (**3.12**) as the second fraction; oil (32%); $^1$H NMR δ 7.79 (s, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.86-1.78 (m, 2H), 1.36 (t, *J* = 7.5 Hz, 2H), 1.36-1.21 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR δ 11.6, 13.8, 19.0, 22.4, 26.3, 28.8 (2C), 29.6, 31.5, 47.9, 150.0, 155.8. Anal. Calcd for $C_{12}H_{23}N_3$: C, 68.85; H, 11.07. Found: C, 68.61; H, 11.35.

1-Octyl-5-pentyl-1,2,4-triazole (**3.13**).

Obtained by lithiation of 1-octyl-1*H*-1,2,4-triazole (**2**) and electrophilic substitution with iodomethane, and purified as mentioned above for compound **3.12** (40%); $^1$H NMR δ 7.79 (s, 1H), 4.04 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.86-1.75 (m, 4H), 1.40-1.27 (m, 14H), 0.94-0.85 (m, 6H); $^{13}$C NMR δ, 13.9, 13.9, 22.2, 22.5, 25.7, 26.5, 27.3, 29.0 (2C), 29.8, 31.3, 31.6, 48.0, 150.1, 155.1. HRMS (EI) 251.2334. Calcd. for $C_{15}H_{29}N_3$ 251.2361.

CHAPTER 4

# ASYMMETRIC INDUCTION USING CHIRAL 1,2,4-TRIAZOLE AND BENZIMIDAZOLE DERIVATIVES

## 4.1 Introduction

Control over the formation of new chiral centers in chiral molecules can be readily achieved, provided that the conformational freedom of the substrate is limited and that preexisting stereochemical elements impose a sufficient degree of asymmetry to the environment of the reaction site.

A wide variety of strategies designed to construct complex chiral targets with reasonable efficiency were developed over the last decade in response to the demands of the production of therapeutically active substances. The most prevalent strategy used is to attach temporarily a "chiral auxiliary" to the achiral substrate. Commonly used auxiliaries include the bicyclic ketones camphor, fenchone and bicyclooctanone. The chirality of the first center in the new chiral compound depends on minimal structural differences between the chiral auxiliaries. For example the two diastereotopic faces of the carbonyl group of camphor are of different accessibility to nucleophilic reagents. Whereas approach to the *endo* face is somewhat impeded by the U-shaped cavity of the molecule, that to the *exo* is strongly hindered by the two methyl groups at C(7). Thus, nucleophilic reagent will attack exclusively from the *endo* side. In the case of fenchone there is less hindrance from the *exo* side than from the *endo*.

1,2,4-Triazole [61CR87] and benzimidazole [74CR279] derivatives possess biological activity which has increased interest in their synthesis and chemical behavior. Recent examples of biological activity include 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles,

which have been found to possess some activity as HIV-1 reverse transcriptase inhibitors [88H1975, 95CA31406, 95CA313807] and fluconazole, a bis-triazole containing compound effective against fungal infections [96COS125].

As shown in the previous chapter (Chapter 3), we have previously synthesized a (*S,S*)-3,5-bis(1-hydroxyethyl)-1,2,4-triazole which gave excellent diastereoselectivities, but contained a chiral auxiliary which was difficult to cleave [96TA1621]. In our continuing efforts to use heterocycles, particularly triazoles, as sources of molecular chirality [96TA1631, 96TA1621], we have now investigated the use of a chiral triazole, to synthesize optically pure alcohols or α-hydroxy ketones. We planned to construct a fused 1*H*,3*H*-oxazolidino[3,4-*a*]-1,2,4-triazole with chirality built into the 5-position of the oxazolidine ring, and to use this optically pure chiral center to induce chirality into the 2-position of the oxazolidine ring (Figure 4.1). Cleavage of the triazole unit with either retention or inversion of configuration could lead to optically pure target molecules. Use of a ketone or aldehyde as an electrophile allows the introduction of further functionality, hopefully with control of both the newly formed chiral centers.

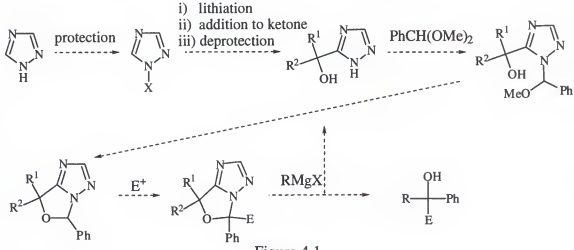


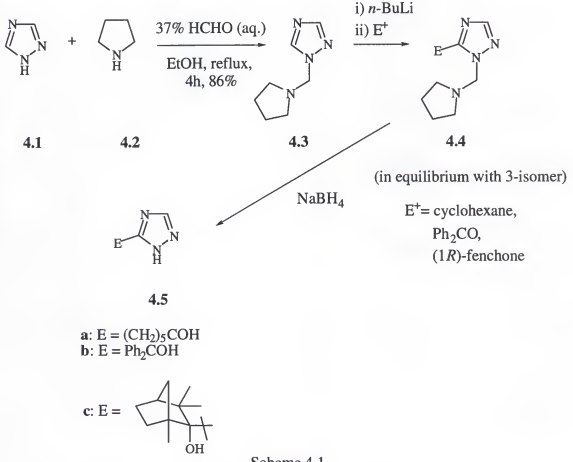

Figure 4.1

## 4.2 Results and Discussion

### 1,2,4-Triazole Approach

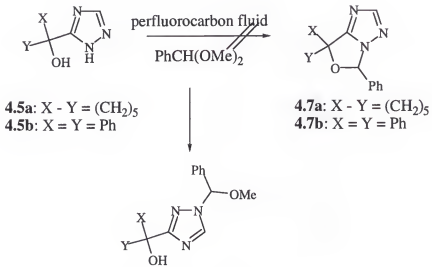
*N*-Substituted 1,2,4-triazoles undergo lithiation and electrophilic attack at the 5-position of the heterocyclic ring [86JHC1257, 90JHC673, 90T641, 93AHC208] although exceptions are known when the electrophile is a benzyl halide [85S302]. Suitable *N*-substituents include benzyl, SEM and aminals such as pyrrolidinomethyl [90T641, 93AHC208, 90T633].

Of these, the pyrrolidinomethyl protecting group was chosen due to its ease of introduction *via* a Mannich-type reaction, and its subsequent ease of removal using sodium borohydride [90T641].



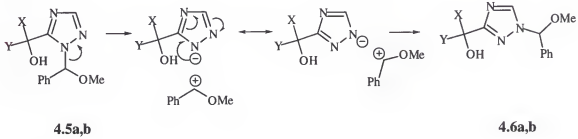

Scheme 4.1

1,2,4-Triazole **4.1** was refluxed with formaldehyde and pyrrolidine **4.2** in ethanol to give the 1-(1-pyrrolidinomethyl)-1,2,4-triazole **4.3** as a colorless oil in 86% yield (Scheme 4.1) [90T641]. The protected triazole was lithiated, using *n*-butyllithium, and quenched with an electrophile. The reactions of the anion derived from **4.3** with cyclohexanone and benzophenone (Scheme 4.1) were performed to test its reactivity against sterically hindered cyclic ketones. Since these alkylations proceeded with good yields, the reaction using camphor, a chiral ketone, was attempted. However, camphor has acidic protons α to the carbonyl group, and the 5-lithiated triazole acted as a base rather than a nucleophile. Such problems are well known and are usually overcome by the use of anhydrous cerium chloride [85TL4763, 94JOC2033, 94TL6713]. We attempted the cerium chloride mediated alkylation, but the yield obtained was unsatisfactory, so fenchone, which does not have any α protons, was chosen as the chiral ketone. This led to **4.5c** as a single diastereoisomer in 69% overall yield (Scheme 4.1).




Scheme 4.2

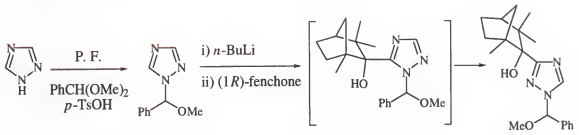
Condensation reactions were attempted with products **4.5** to form bicyclic ring structures. Benzaldehyde dimethyl acetal, with or without an acid catalyst or molecular sieves, in refluxing performance fluid, gave hemiaminals **4.6a** and **4.6b** from **4.5a** or **4.5b** respectively (Scheme 4.2). However, none of the desired bicycles **4.7a,b** were formed. This is believed to be due to the equilibrium that was shown to exist between certain 3- and 5-substituted triazoles [93AHC208, 90T633]. The 3-substituted triazole shown to be the more stable of these tautomers cannot cyclize to form the bicycle (Scheme 4.3).



**4.5a,b** **4.6a,b**

Scheme 4.3

We attempted to overcome this problem by first introducing the hemiacetal onto the 1-position of the triazole and then carrying out the lithiation in the 5-position as previously described with fenchone as the chiral auxiliary. It was hoped that the resulting oxygen anion would then undergo nucleophilic attack at the α-carbon thus, displacing methanol and forming the bicycle in one-step. The first two reaction steps succeeded, but no nucleophilic displacement of methanol occurred. Probably, the initial product **4.9a** rearranged rapidly into the alcohol **4.9b** (Scheme 4.4).



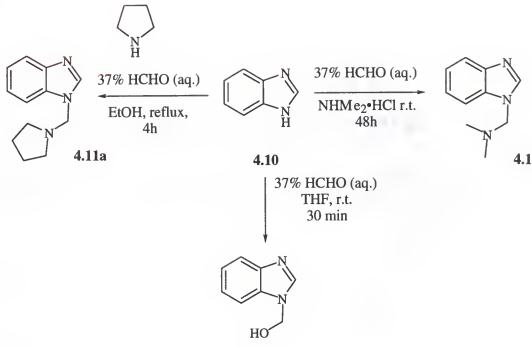

**4.1** **4.8** **4.9a** **4.9b**

Scheme 4.4

Attempts at (i) nucleophilic displacement of the *N*-substituent of the triazole **4.9b** with a Grignard reagent and (ii) lithiation of the CH group both failed and we therefore, transferred our efforts from the 1,2,4-triazole to the benzimidazole system.

Benzimidazole Approach

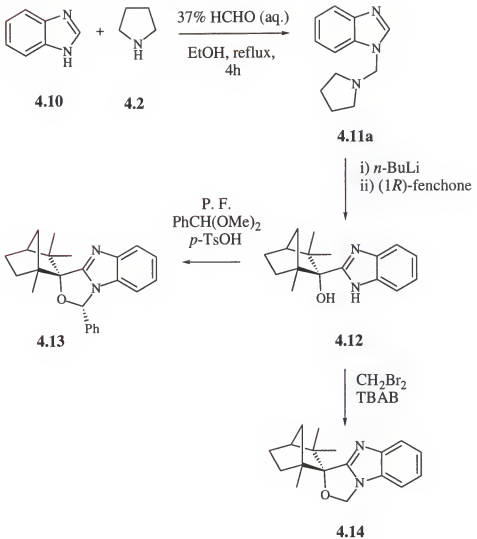
Since it was believed that isomerization was taking place between the 1,5-substituted and 1,3-substituted triazoles, with the 1,3-substituted being more stable, we decided to use benzimidazole as the heterocycle, where such isomerization is not possible. Like triazoles, benzimidazoles are known to readily undergo ring lithiation in the 2-position provided a suitable group protects the nitrogen atom [74CR279, 88JOC5685, 89JOC2949]. Protecting groups investigated were dimethylaminomethyl [88JOC5685], hydroxymethyl [89JOC2949] and pyrrolidinomethyl [90TL641]. The best results were obtained in the last case (better yield and facile deprotection step).




Scheme 4.5

The pyrrolidinomethyl protecting group was introduced onto benzimidazole **4.10** to give **4.11a** in 80% yield [90JHC673]. Lithiation, followed by electrophilic substitution using (1*R*)-fenchone as the electrophile and an acidic work-up, gave directly the deprotected benzimidazole **4.12** as a single diastereoisomer in 70% yield (Scheme 4.6).

Ring closure using benzaldehyde dimethyl acetal in refluxing performance fluid using catalytic *p*-toluenesulfonic acid proceeded well to yield the novel tricycle **4.13** as a single diastereoisomer in 51% yield (Scheme 4.5).

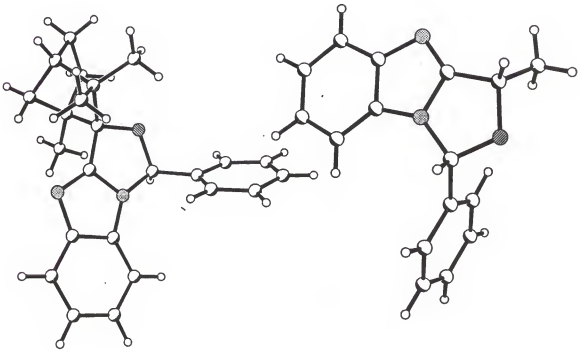



Scheme 4.6

To establish unambiguously the relative stereochemistry in **4.13**, a single crystal X-ray structure was obtained. Compound **4.13** crystallizes with two independent molecules in the asymmetric unit, one of which is shown in Scheme 4.6. The two independent molecules differ only in the torsional orientation of the phenyl ring which is inclined to the plane of the oxazolidine ring at angles of 65.2° and 88.6° in the two molecules. This structure determination confirms the structures of both **4.12** and **4.13** and establishes the configuration of the spiro center as *R* and the newly formed stereocenter as *S*. There are no unusual bond lengths or angles in this structure, which represents the first

X-ray determination of an oxazolidino[3,4-a]benzimidazole. Attack at the *exo* face of the carbonyl group in fenchone is consistent with known reactions of aryl lithium reagents with fenchone [79AJC2441].

However, attempts to displace the benzimidazole residue in **4.13** using a Grignard reagent failed. Lithiation occured at the α-CH group, as shown by the epimerization at the newly formed chiral center, but attempts to introduce a methyl group by reaction of the anion with methyl iodide also failed.



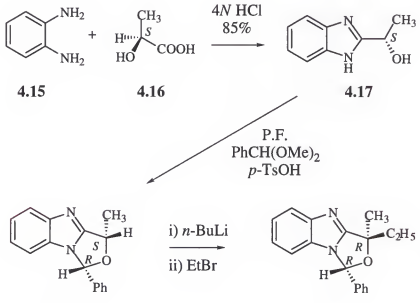
Scheme 4.7. X-Ray crystal structure of one of the independent molecules of **4.13**.

Scheme 4.8. X-Ray crystal structure of **4.18**.

It was believed that steric hindrance was the reason for electrophilic attack not taking place on the anion of **4.13** other than by a proton, and so it was decided to synthesize the tricycle **4.14** with a methylene group at position 2 which would hopefully, facilitate the introduction of other electrophiles into this position. Chiral benzimidazole

**4.12** reacted with dibromomethane in the presence of tetrabutylammonium bisulfate, as a phase transfer catalyst, to yield the desired tricycle **4.14** in 70% yield (Scheme 4.6). However, attempts to lithiate compound **4.14** failed, probably due to the low acidity of the methylene group.

Another way to relieve possible steric hindrance to lithiation at the 2-position is to reduce the size of the chiral auxiliary. We therefore, replaced the fenchone group by reacting *o*-phenylenediamine **4.15** with (*S*)-lactic acid **4.16** to form **4.17** [28JCS2393, 90H1245] (Scheme 4.9). Condensation of **4.17** with benzaldehyde dimethyl acetal gave **4.18** as a single diastereoisomer in 50% yield. NOE measurements and X-ray crystal structure determination (Scheme 4.8) confirmed that the methyl and phenyl groups are on the same side of the molecule. Thus, the newly formed chiral center has the *R* configuration in this case. Once again the orientation of the phenyl ring is orthogonal to the oxazolidine ring (angle between meanplanes = 84.4°).




Scheme 4.9

Lithiation of compound **4.18** with *n*-butyllithium followed by quenching with ethyl bromide gave **4.19** as a single diastereoisomer in 72% yield. This corresponds to substitution at the 5-position of the oxazole ring (Scheme 4.9: in **4.18** the proton at the 5-position of the oxazole ring is evidently more acidic than that in the 2-position [85S302]. As it will be demonstrated by the NOEDIF experiments presented in the next chapter (Chapter 5), the lithiation took place with retention of configuration to give the diastereoisomer shown.

We conclude that the rapid isomerization of certain *N*-substituents in C-monofunctionalized 1,2,4-triazoles renders problematic ring closure to form sterically constrained bicycles. The novel 5(*S*)-methyl-2(*R*)-phenyl-1*H*,3*H*-oxazolo[3,4-*a*] benzimidazole **4.18** proved to be an useful precursor for the syntheses of other enantiomerically pure chiral derivatives, as it will be shown in the next chapter (Chapter 5).

## 4.3 Experimental Part

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a Gemini 300 MHz spectrometer; *J* values are given in Hz. Elemental analyses were performed on a Carlo Erba-1106 instrument. $[\alpha]_D$ were recorded on a Perkin Elmer 341 polarimeter. Tetrahydrofuran was predried and freshly distilled from sodium and benzophenone. Column chromatography was carried out on silica gel (230-400 mesh).

1-(1-Pyrrolidinomethyl)-1,2,4-triazole (**4 .3**).

1,2,4-Triazole (7.81 g, 0.11 mol), pyrrolidine (8.5 g, 0.12 mol) and a 37% solution of formaldehyde in water (10 mL, 0.12 mol) were dissolved in ethanol (50 mL). The mixture was refluxed for 4 h. and the solvent removed under vacuum. The resulting residue was diluted with water and extracted with chloroform (3 x 25 mL) before drying over anhydrous $Na_2SO_4$. This was filtered, concentrated and the resulting oil distilled under vacuum (100°C/1.2 torr) to give compound **4.3** as a colorless oil in 86% yield [90T641]. δ ($CDCl_3$): 8.15 (1H, s), 7.95 (1H, s), 5.14 (2H, s), 2.74-2.69 (4H, m), 1.79-1.74 (4H, m); δ ($CDCl_3$): 151.3, 143.2, 66.3, 49.5, 23.6.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-pyrrolidinomethyl)-1,2,4-triazole (**4 .4b**)

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **3** (760 mg, 5 mmol) was dissolved in dry THF (50 mL) under argon and cooled to -78°C before adding *n*-butyllithium (2.2 *M*, 2.5 ml, 1.1 equiv.) dropwise. The mixture was stirred at -78°C for 1 h. before adding benzophenone (5 mmol, 1 equiv.) in THF (10 ml). After addition was complete the mixture was maintained at -78°C for a further 1 h. before allowing it to warm to room temperature overnight. The mixture was extracted with diethyl ether and washed with saturated ammonium chloride solution (50 ml), dried and evaporated to dryness to give the mixture of 3- and 5-isomers in a ratio of 1 : 1as a white solid. Yield = 80%, m.p. 121-122 °C. $\delta_H$($CDCl_3$): 8.71 (1H, br. s, (5)), 8.06 (1H, s, (3)), 7.77 (1H, s, (5)), 7.45-7.24 (20H, m), 5.07 (2H, s, (3)), 4.57 (1H, br. s, (3)), 4.44 (2H, s, (5)), 2.71-2.66 (4H, m, (3)), 2.50-2.48 (4H, m, (5)), 1.85-1.79 (4H, m, (5)), 1.79-1.71 (4H, m, (3)); δ $_C$($CDCl_3$): 167.8, 160.5, 148.8, 145.3, 143.8, 143.7, 128.0, 127.7, 127.5, 127.4,

127.2, 126.9, 77.8, 76.3, 69.0, 66.7, 50.9, 49.7, 23.9, 23.3. For $C_{20}H_{22}N_4O$: Anal. Calcd: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.36; H, 6.69; N, 16.76.

3(5)-(1-Hydroxycyclohexyl)-1,2,4-triazole (**4.5a**)

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **3** (1 g, 6.6 mmol) was dissolved in THF (50 mL) and cooled to -78°C. This was then treated with *n*-butyllithium (2.0 *M*, 3.5 mL, 7 mmol, 1.05 equiv.) and stirred for 2 h. before adding cyclohexanone (0.7 g, 7.1 mmol, 1.1 equiv.). The mixture was maintained at -78°C for a further 4 h. before allowing it to warm to room temperature overnight. This was then quenched with saturated ammonium chloride solution (100 mL) and extracted with diethyl ether (2 x 50 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the pure product as a white solid in 63% yield. m.p. 184°C, (lit. [90T641] 183-185°C); δ ($CDCl_3$): 13.75 (1H, br. s), 7.97 (1H, br. s), 5.26 (1H, br. s), 2.10-1.12 (10H, m); δ ($d_6$-DMSO): 164.0, 149.1, 68.9, 36.9, 25.1, 21.4.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1,2,4-triazole (**4.5b**)

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-pyrrolidinomethyl)-1,2,4-triazole **4.4b** (5 g, 0.015 mol) was dissolved in ethanol and treated with sodium borohydride (0.57 g, 0.015 mol, 1 equiv.) and refluxed for 2 h. Removal of the ethanol, under reduced pressure, was followed by refluxing the residue in ethyl acetate overnight. The solution was then dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give the product in 70% yield. m.p. 116°C; δ ($d_6$-DMSO): 13.93 (1H, s), 7.93 (1H, br. s),

7.53-7.20 (10H, m), 7.00 (1H, br. s); δ ($d_6$-DMSO): 160.5 151.0, 145.5, 127.6, 127.1, 76.9 (the signal of one carbon of the triazole ring is not observed). For $C_8H_{13}N_3O$: Anal. Calcd: C, 57.45; H, 7.84; N, 25.13. Found: C, 57.79; H, 8.02; N, 25.37.

3(5)-[2-(2(*S*)-Hydroxy-1(*R*),3,3-trimethyl[2.2.1]heptyl)]-1,2,4-triazole (**4.5c**)

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **4.3** (2.3 g, 0.015 mol) was dissolved in THF (50 mL) and cooled to -78°C. This was then treated with *n*-butyllithium (2.0 *M*, 7.5 mL, 0.016 mol) and stirred for 2 h. before adding (1*R*)-fenchone (2.4 mL, 0.016 mol). The mixture was maintained at -78°C for a further 4 h. before allowing it to warm to room temperature overnight. This was then quenched with saturated ammonium chloride solution and extracted with diethyl ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the crude product which, when washed with cold diethyl ether, afforded the pure product as a white solid in 69% yield. m.p. 117°C, $[\alpha]_D$=14.7 at 30°C (c = 0.01 g/mL, methanol); δ ($d_6$-DMSO): 7.90 (1H, br. s), 4.94 (1H, br. s), 2.69 (1H, d, *J* = 9 Hz), 2.09-2.01 (1H, m), 1.71-1.65 (2H, m), 1.46-1.34 (1H, m), 1.13 (1H, d, *J* = 9 Hz), 1.02 (1H, dt, *J* = 12, 3 Hz), 0.94 (6H, d, *J* = 6 Hz), 0.50 (3H, s); δ ($d_6$-DMSO): 160.3, 150.2, 81.7, 52.9, 48.0, 45.2, 40.5, 29.4, 28.0, 25.2, 22.0, 17.1. For $C_{12}H_{19}N_3O$: Anal. Calcd: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.13; H, 8.78; N, 19.15.

General Procedure for Formation of Hemiacetals (**4.6a**) and (**4.6b**)

Benzaldehyde dimethyl acetal (3 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of **4.5a** or **4.5b** (0.01 mol) in dry toluene

and then refluxed for 24 h. using a reverse Dean-Stark. The reaction mixture was then cooled and the solvent was removed under vacuum to give the desired product as a white solid.

3(5)-(1-Hydroxycyclohexyl)-1-(1-methoxy-1-phenylmethyl)-1,2,4-triazole (**4 ,6a**)

Yield = 43%, m.p. 110°C; δ ($d_6$-DMSO): 8.59 (1H, s), 7.42-7.38 (5H, m), 6.54 (1H, s), 4.84 (1H, s), 3.34 (3H, s), 2.00-1.94 (2H, m), 1.72-1.62 (4H, m), 1.41-1.29 (4H, m); δ ($d_6$-DMSO): 169.5, 144.0, 137.2, 128.8, 128.3, 126.3, 89.3, 68.9, 56.1, 36.8, 25.2, 21.9. For $C_{16}H_{21}N_3O_2$: Anal. Calcd: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.65; H, 7.48; N, 14.59.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-methoxy-1-phenylmethyl)-1,2,4-triazole (**4 ,6b**)

Yield = 36%, m.p. 120°C; $\delta_H$($d_6$-DMSO): 8.70 (1H, s), 7.43-7.18 (15H, m), 6.58 (1H, s), 6.42 (1H, s), 3.37(1H. s); $\delta_C$($d_6$-DMSO): 168.3, 146.4, 146.3, 144.2, 137.0, 128.9, 128.4, 127.3, 127.1, 126.6, 126.3, 89.5, 77.0, 56.2. For $C_{23}H_{21}N_3O_2$: Anal. Calcd: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.43; H, 5.73; N, 11.33.

1-(1-Methoxy-1-phenylmethyl)-1,2,4-triazole (**4 ,8**)

1,2,4-Triazole (6.9 g, 0.1 mol) and benzaldehyde dimethyl acetal (22.8 g, 0.15 mol, 1.5 equiv.) were refluxed in performance fluid using a reverse Dean-Stark with a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was cooled and the solvent removed under reduced pressure to give the crude product, which was purified by Kugelrohr distillation to give **8** in 89% yield. m.p. 50°C (lit. [90T641] b.p. 150°C). δ

($CDCl_3$): 8.16 (1H, s), 8.01 (1H, s), 7.40-7.38 (5H, m), 6.40 (1H, s), 3.50 (3H, s); δ ($CDCl_3$): 151.4, 142.1, 136.2, 129.4, 128.6, 125.9, 90.9, 57.1.

1-(1-Methoxy-1-phenylmethyl)-5-[2-(2(*S*)-hydroxy-1(*R*),3,3-trimethyl[2.2.1]- heptyl)]-1,2,4-triazole (**4 .9**)

A solution of compound**4. 8** (0.02 mol, 3.78 g) was dissolved in THF and cooled to -78°C. This was treated with 2.2 M *n*-butyllithium (0.022 mol, 10 mL), dropwise. The resulting mixture was stirred at -78°C for 2 h. before quenching with (1*R*)-fenchone (0.02 mol, 3.1 g). The reaction mixture was maintained at this temperature for a further 2 h. before being allowed to warm to room temperature overnight. This was quenched with saturated ammonium chloride solution, extracted with diethyl ether and dried over anhydrous magnesium sulfate. The mixture was filtered and evaporated to dryness to give the pure product as a single diastereoisomer in 70% yield as a white solid. m.p. 72-74°C, $[\alpha]_D$=-16.4 at 30°C (c=0.01 g/mL, chloroform); δ ($CDCl_3$): 7.88 (1H, s), 7.36-7.27 (5H, m), 7.07 (1H, s), 3.50 (3H, s), 2.95-2.91 (1H, m), 2.84-2.82 (1H, m), 1.93-1.86 (1H, m), 1.76-1.66 (1H, m), 1.58 (1H, s), 1.52-1.41 (1H, m), 1.29-1.11 (2H, m), 1.05 (6H, s), 0.94 (3H, s); δ ($CDCl_3$): 158.5, 149.2, 137.5, 128.6, 128.2, 126.5, 91.3, 84.2, 56.7, 54.8, 48.8, 46.2, 46.2, 40.6, 30.4, 28.3, 24.8, 22.0, 17.1. HRMS (POS FAB NBA) m/e 342.2190 (M+1). Calcd. For $C_{20}H_{28}O_2N_3$ 342.2181.

1-(1-Pyrrolidinomethyl)benzimidazole (**4 .11a**)

Benzimidazole (3.5 g, 0.03 mol), pyrrolidine (2.1 g, 0.03 mol) and a 37% solution of formaldehyde in water (2.7 g, 0.03 mol) were dissolved in ethanol (50 mL). The

mixture was refluxed for 4 h. and then the solvent was removed under vacuum. The resulting residue was diluted with water and extracted with chloroform (3 x 25 mL) before drying over anhydrous $Na_2SO_4$. This was then filtered and concentrated and the resulting oil was distilled under vacuum (110°C/5 mmHg) to give compound **4.11a** as a colorless solid in 80% yield. m.p. 25°C [18]; $\delta_H(CDCl_3)$: 7.90 (1H, s), 7.81-7.77 (1H, m), 7.49-7.46 (1H, m), 7.28-7.25 (2H, m), 4.98 (2H, s), 2.63-2.59 (4H, m), 1.75-1.70 (4H, m); $\delta_C(CDCl_3)$: 143.4, 143.3 134.4, 122.9, 122.0, 120.0, 110.1,
62.8, 50.6, 23.5.

1-(Hydroxymethyl)benzimidazole (**4.11b**)

Benzimidazole (3.5g, 0.03 moles) and aqueous formaldehyde solution (37%, 2.7g, 0.3 moles) were mixed and dissolved in 50 ml THF. After 5 min. the solvent was removed, the residue washed with ether and dried in vacuo for 24h. Yield 91%; [89JOC2949] m.p. 140°C [18]; $\delta_H$(DMSO): 8.27 (s, 1H), 7.66 (d, $J$ = 7.5 Hz, 2H), 7.30-7.19 (m, 2H), 6.72 (t, $J$ = 7.5 Hz, 1H), 5.60 (d, $J$ = 7.5 Hz, 2H); $\delta_C$(DMSO): 143.9, 143.7, 133.3, 122.5, 121.8, 119.4, 110.9, 67.4.

1-[(Dimethylamino)methyl]benzimidazole (**4.11c**)

Benzimidazole (3.5 g, 0.03 moles) and 97% dimethylamine hydrochloride (2.6 g, 0.03 moles) were dissolved in water (40 ml) and concentrated HCl added until pH = 5. Aqueous formaldehyde solution (37%, 2.7 g, 0.3 moles) was added and the mixture was allowed to stir at r.t. for 48h. The solution was made strongly alkaline with KOH sol. 20% and the organic material was treated with $K_2CO_3$ and extracted with chloroform. The

combined organic layers were dried ($MgSO_4$) and concentrated to give an oil which was distilled under vacuum, b.p. 90°C (5mmHg). Yield 80%. $\delta_H(CDCl_3)$: 7.90 (s, 1H), 7.81-7.78 (m, 1H), 7.49-7.46 (m, 1H), 7.31-7.24 (m, 2H), 4.79 (s, 2H), 2.30 (s, 6H) ; $\delta_C(CDCl_3)$: 143.4, 143.3, 134.3, 122.9, 122.0, 119.9, 110.2, 67.2, 42.2.

2-[2-(2(*S*)-Hydroxy-1(*R*),3,3-trimethyl[2.2.1]heptyl)]benzimidazole (**4.12**)

1-(1-Pyrrolidinomethyl)benzimidazole **4.11** (3 g, 0.015 mol) was dissolved in THF (50 mL) under argon and cooled to -78°C before treating with 2.0 M *n*-butyllithium (7.5 mL, 0.016 mol), dropwise. The resulting mixture was kept at this temperature for 2 h. before quenching with (1*R*)-fenchone (2.4 mL, 0.016 mol). This was then maintained at -78°C for a further 4 h. before allowing to warm to room temperature overnight. The mixture was acidified with 2*N* hydrochloric acid and this was washed with diethyl ether. The aqueous phase was then neutralized with sodium bicarbonate and then extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. Column chromatography of the crude material on silica gel using hexane:diethyl ether (1:1) as eluant gave the pure material as a white solid in 70% yield. m.p. 187°C, $[\alpha]_D$=-27.7 at 27°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 9.55 (1H, br. s), 7.77-7.74 (1H, m), 7.42-7.39 (1H, m), 7.25-7.18 (2H, m), 2.81(1H, s), 2.85 (1H, s), 1.96-1.75 (3H, m), 1.59-1.48 (1H, m), 1.39 (1H, d, $J$ = 10.8 Hz), 1.27 (1H, dt, $J$ = 12.9, 3.6 Hz), 1.05 (6H, d, $J$ = 3.3 Hz), 0.74 (3H, s); $\delta_C(CDCl_3)$: 157.3, 143.1, 132.3, 122.3, 121.7, 119.4, 110.5, 83.8, 53.3, 48.4, 45.9, 41.2, 30.2, 28.2, 25.1, 22.0, 17.1. For $C_{17}H_{22}N_2O$: Anal. Calcd: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.60; H, 8.35; N, 10.16.

Spiro[1(*R*),3,3-trimethyl[2.2.1]heptyl-2(*S*),5'-2'(*S*)-phenyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole] (**4.13**)

Benzaldehyde dimethyl acetal (3 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of **4.12** (2.7 g, 0.01 mol) in dry toluene and then refluxed for 24 h. using a reverse Dean-Stark. The reaction mixture was then cooled and the solvent was removed under vacuum to give a crude product which was columned on silica gel using a 1:1 mixture of hexane:diethyl ether as eluant to give pure **4.13** as a white solid in a 51% yield. m.p. 121°C, $[\alpha]_D$=-4.6 at 28°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.83 (1H, d, *J* = 8.1 Hz), 7.45-7.36 (5H, m), 7.23 (1H, t, *J* = 7.2 Hz), 7.08 (1H, t, *J* = 7.3 Hz), 6.85 (1H, d, *J* = 8.1 Hz), 6.62 (1H, s), 2.63 (1H, d, *J* = 10.2 Hz), 2.16-2.09 (1H, m), 1.89-1.79 (2H, m), 1.54-1.48 (1H, m), 1.32-1.26 (2H, m), 1.22 (3H, s), 0.90 (3H, s), 0.81 (3H, s); $\delta_C(CDCl_3)$: 160.0, 149.4, 137.0, 130.2, 129.6, 128.9, 127.1, 122.2, 122.1, 120.2, 109.8, 93.2, 88.2, 54.0, 48.3, 43.9, 40.4, 28.9, 28.6, 26.1, 23.4, 17.5. For $C_{24}H_{26}N_2O$: Anal. Calcd: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.50; H, 7.47; N, 7.66.

Spiro[1(*R*),3,3-trimethyl[2.2.1]heptyl-2(*S*),5'-1*H*,3*H*-oxazolo[3,4-*a* benzimidazole] (**4.14**)

A solution of compound **4.12** (1 g, 3.7 mmol) in methylene bromide was refluxed overnight with a 40% aqueous solution of sodium hydroxide (40 mL) in the presence of a catalytic amount of tetrabutylammonium bisulfate. The crude product was isolated by separating the organic layer and evaporating it to dryness. Column chromatography on silica gel using a 1:2 mixture of hexane/diethyl ether gave the pure product as a white solid in 50% yield. m.p. 179-180°C, $[\alpha]_D$=-218.5 at 29°C (c=0.01 g/mL, chloroform); δ

$_H$($CDCl_3$): 7.74 (1H, d, $J$ = 7.8 Hz), 7.32 (s, 1H), 7.25 (s, 1H), 7.13 (1H, t, $J$ = 8.1 Hz), 6.94 (1H, t, $J$ = 7.2 Hz), 6.57 (1H, d, $J$ = 8.1 Hz), 3.12 (1H, br. d, $J$ = 9.5 Hz), 2.29 (1H, s), 1.90-1.72 (4H, m), 1.57-1.09 (7H, m), 0.66 (3H, s); $\delta_C$($CDCl_3$): 155.6, 142.0, 134.7, 123.0, 122.1, 120.1, 110.7, 85.1, 57.8, 55.2, 49.7, 45.9, 41.0, 31.3, 27.9, 25.0, 22.6, 17.7. HRMS (POS FAB NBA) m/e 283.1809 (M+1). Calcd. For $C_{18}H_{23}ON_2$ 283.1810.

(*S*)-2-(1-Hydroxyethyl)benzimidazole (**4.17**)

*o*-Phenylene diamine (2.16 g, 0.02 mol), (*S*)-lactic acid (2.7 g, 0.03 mol) and 4*N* hydrochloric acid (20 mL) were heated under reflux for 40 min. The solution was then filtered and neutralized with ammonia to afford the product as a brownish solid which when recrystallised from ethanol gave pure **4.17** as a white solid in 85% yield. m.p. 180-182°C (lit. [21] 178-179°C), $[\alpha]_D$=-34.1 at 30°C (c=0.01 g/mL, methanol); $\delta_H$($d_6$-DMSO): 12.3 (1H, br. s), 7.53-7.50 (2H, m), 7.15-7.13 (2H, m) 5.89 (1H, br. s), 5.03-4.97 (1H, m), 1.55 (3H, d, $J$ = 6 Hz); $\delta_C$($d_6$-DMSO): 158.7, 142.6, 121.3, 117.2, 63.8, 23.0. For $C_9H_{10}N_2O$: Anal. Calcd: C, 66.63; H, 6.22; N, 17.28. Found: C, 66.73; H, 6.31; N, 17.36.

5(*S*)-Methyl-2(*R*)-phenyl-1*H*,3*H*-oxazolo[3,4-a]benzimidazole (**4.18**)

(*S*)-2-(1-Hydroxyethyl)benzimidazole **4.17** (1.5 g, 9.3 mmol), benzaldehyde dimethyl acetal (1.4 g, 9.2 mmol) and a catalytic amount of *p*-toluenesulfonic acid were refluxed in performance fluid (5080) for 24 h., using a reverse Dean-Stark. The reaction mixture was then allowed to cool before removing the solvent and purifying the product by Kugelrohr distillation. Yield = 50%, m.p. 141-142°C, $[\alpha]_D$=145.8 at 26°C (c=0.01

g/mL, chloroform); $\delta_H(CDCl_3)$: 7.75 (1H, d, $J$ = 9 Hz), 7.45 (5H, s), 7.22 (1H, t, $J$ = 9 Hz), 7.07 (1H, t, $J$ = 9 Hz), 6.79 (1H, d, $J$ = 9 Hz), 6.59 (1H, s), 5.39 (1H, q, $J$ = 6 Hz), 1.82 (3H, d, $J$ = 6 Hz); $\delta_C(CDCl_3)$: 159.7, 149.3, 135.3, 130.5, 130.3, 129.0, 127.3, 122.5, 122.4, 120.1, 109.9, 88.8, 72.3, 19.4. For $C_{16}H_{14}N_2O$: Anal. Calcd: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.56; H, 5.88; N, 11.30.

5(*R*)-Ethyl-5-methyl-2(*R*)-phenyl-1*H*,3*H*-oxazolo[3,4-*a*] benzimidazole (**4.19**)

A solution of 5-methyl-2-phenyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole **4.18** (0.2 g, 0.8 mmol) in THF, under argon, was cooled to -78°C before being treated with *n*-butyllithium (1.6 *M*, 0.55 mL, 0.88 mmol, 1.1 equiv.), dropwise. The temperature of the mixture was maintained at -78°C for 2 h. before adding ethyl bromide (870 mg, 0.8 mol, 1 equiv.). This was stirred for a further 2 h. at -78°C before being allowed to warm to room temperature overnight. The reaction was then quenched with saturated ammonium chloride solution and extracted with diethyl ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the crude product as a white solid. Column chromatography on silica gel using a 1:2 mixture of hexane:diethyl ether as eluant gave the pure product in 72% yield. m.p. 122-124°C, $[\alpha]_D$=103.0 at 30°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.75 (1H, d, $J$ = 6 Hz), 7.43 (5H, s), 7.23 (1H, t, $J$ = 6 Hz), 7.08 (1H, t, $J$ = 6 Hz), 6.85 (1H, d, $J$ = 6 Hz), 6.70 (1H, s), 2.07 (2H, q, $J$ = 6 Hz), 1.82 (3H, s), 1.01 (3H, t, $J$ = 6 Hz); $\delta_C(CDCl_3)$: 161.4, 149.4, 136.2, 130.3, 130.3, 129.0, 127.1, 122.4, 122.4, 120.1, 110.0, 88.5, 82.6, 32.9, 25.4, 8.4.

X-Ray Crystallography

Intensity data were collected with a Nicolet P4s four-circle diffractometer, operating at -110°C, using monochromatized Mo Kα (l = 0.71073 Å) radiation. Cell constants were determined by least-squares refinements of at least 34 accurately centered reflections. Throughout the data collections the intensities were monitored at regular intervals and the intensities were corrected for minor fluctuations (<6%). The intensities were also corrected for Lorentz and polarization effects, but not for absorption.

The structures were solved by direct methods using SHELXS90 [90AC(A)467], and refined on $F^2$, using all data, by full-matrix least-squares procedures using SHELXL93 [93MI1]. All non-hydrogen atoms were refined with anisotropic displacement coefficients equal to 1.3 times the isotropic equivalent of their carrier carbons. The functions minimized were $\Sigma w(F_o^2-F_c^2)$, with $W = [\sigma^2(F_o^2) + aP^2]^{-1}$, where $P = [\max(F_o^2) + 2F_c^2]/3$. Final difference maps showed no features greater or less than 0.29e⁻/ Å$^3$.

*Crystal data for* ***4.13*** *-at 110°C*: $C_{24}H_{26}N_2O$, Mr = 358.5, colorless block, 0.69 x 0.54 x 0.21 mm, triclinic, space group P1, $a$ = 9.675(1), $b$ = 9.796(2), $c$ = 11.984(1) Å, α = 76.92(1), β = 73.72(1)°, γ = 65.20(1), U = 982.0(2) Å$^3$, F(000) = 384, Z = 2, $D_c$ = 1.212 g cm$^{-3}$, μ(Mo-Kα) = 0.74 cm$^{-1}$, ω scans, $2\theta_{max}$ = 50°, 487 parameters, S = 0.94, wR2 = 0.1441 for all 3667 data, (a = 0.098), R1 = 0.0544 for 2690 data with $F_o>4\sigma(F_o)$.

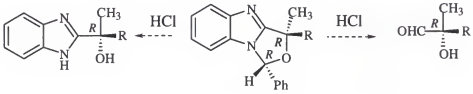
*Crystal data for* ***4.18*** *-at 110°C*: $C_{16}H_{14}N_2O$, Mr = 250.3, colorless rod, 0.96 x 0.29 x 0.14 mm, orthorombic, space group $P2_12_12_1$, $a$ = 4.848(3), $b$ = 9.579(3), $c$ = 27.643(8) Å, U = 1284(1) Å$^3$, F(000) = 528, Z = 4, $D_c$ = 1.295 g cm$^{-3}$, μ(Mo-Kα) = 0.82 cm$^{-1}$, ω scans, $2\theta_{max}$ = 50°, 172 parameters, S = 0.87, wR2 = 0.1552 for all 1356 data, (a = 0.081), R1 = 0.0592 for 763 data with $F_o>4\sigma(F_o)$.

CHAPTER 5

# ASYMMETRIC SYNTHESIS OF 2-(α-HYDROXYALKYL)-BENZIMIDAZOLES

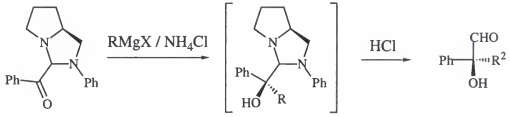
## 5.1 Introduction

The novel 5(*S*)-methyl-2(*R*)-phenyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole **4.18** presented in the previous chapter (Chapter 4) could be used as the precursor for the syntheses of various chiral compounds. The acidic hydrolysis of substituted 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles could cleave the oxazole and benzimidazole rings to give the α-hydroxy aldehydes or could displace the benzaldehyde unit to yield 2-(α-hydroxyalkyl)-benzimidazoles.




Scheme 5.1

According to Mukaiyama [78CL1253, 81T4111], α-hydroxy aldehydes are readily obtained *via* acidic hydrolysis of hemiaminals under mild reaction conditions.




Scheme 5.2

2-(α–Hydroxybenzyl)benzimidazoles and related 2-(α-hydroxyalkyl)-benzimidazoles are compounds with high biological potential, as shown by the numerous reports on their various physiological actions: respiratory, analeptic, analgesic, spasmolytic, antiinflammatory and antihypertensive [69N785, 73CA137156, 76CA135655, 87CA18565]. QSAR studies and biological tests demonstrated that, of the two optical isomers of 2-(α-hydroxybenzyl)benzimidazole derivatives, the D enantiomer is more active and selective than the L-enantiomer [64N639]. Previous synthetic approaches to 2-(α-hydroxybenzyl)benzimidazoles have involved lithiation of an N-protected benzimidazole, followed by the electrophilic attack of a carbonyl compound [68CA68992, 72CA34326, 87JCS(P1)2787] or direct reaction of a benzimidazole with a ketone [87CA18565], these approaches provide the products as racemic mixtures .

We now report the synthesis of enantiomerically pure 2-(α-hydroxyalkyl)-benzimidazoles **5.6b-d** utilizing 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles **5.5b-d** as key intermediates, themselves derived from chiral (*R* or *S*) 2-(α-hydroxyethyl)benzimidazole **5.3** obtained from *o*-phenylenediamine **5.1** and the appropriate enantiomer of lactic acid (*R* or *S*) **5.2**.

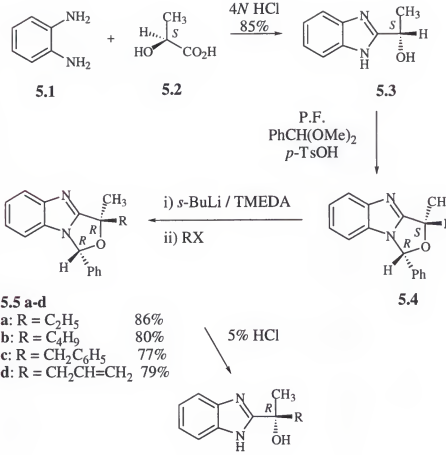
The second objective of our project was to obtain the above mentioned α-hydroxy aldehydes from 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles **5.5b-d**. As it will be shown further the stability of the benzimidazole ring compared to the hemiaminal ring stops the acidic hydrolysis to the 2-(α-hydroxyalkyl)benzimidazole stage.

## 5.2 Results and Discussion

### Synthesis of 5(*R*)-Alkyl-5-methyl-2(*R*)-phenyl-1H,3H-oxazolo[3,4-*a*]-benzimidazoles and 2-(α-Hydroxyalkyl)benzimidazoles

We previously obtained excellent diastereoselectivities in the synthesis of 5-methyl-5-ethyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole **5.5a** by this route [97TA1491]. Condensation of **5.3** (obtained from *o*-phenylenediamine **5.1** with (*S*)-lactic acid **5.2**) with benzaldehyde dimethyl acetal in refluxing perfluorocarbon fluid using catalytic *p*-toluenesulfonic acid, (Chapter 4, **4.17**) [97TA1491], yielded 50% of compound **5.4** as a single diastereoisomer. As before [97TA1491], lithiation of compound **5.4** with *s*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), followed by quenching with ethyl bromide gave compound **5.5a** as a single diastereoisomer and novel compounds **5.5b-d** were obtained similarly in yields of 78-80%. Thus this lithiation at the 5-C of the oxazole ring proceeded by the attack of the electrophile with retention of configuration (Scheme 5.3). NOEDIF measurements together with earlier X-ray findings for compounds **5.4** and **5.5a** [97TA1491] prove that the newly formed chiral center has a *R* configuration, as is further discussed below.

The analysis of the $^1$H-NMR and GC-MS spectra of the crude reaction mixtures of products **5.5a-d** showed that the isomers of **5.5a-d** with inverted configuration were formed in less than 5%, and substitution in position 2 does not occur. However, the regioselectivity of the method does not prove a higher thermodynamic acidity of the proton attached to 5-C, as steric effects may be involved. The diastereoselectivity is strongly influenced by the molarity of the reaction mixture: while the reaction is diastereospecific at a $8x10^{-3}$M concentration of reagents, at $2x10^{-2}$M the reaction ceases to be diastereoselective, the observed ratio of diastereomers at this concentration is 1 : 1.




**5.1** **5.2** **5.3**

**5.5 a-d**
**a**: R = $C_2H_5$ 86%
**b**: R = $C_4H_9$ 80%
**c**: R = $CH_2C_6H_5$ 77%
**d**: R = $CH_2CH{=}CH_2$ 79%

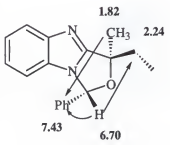
**5.4**

**5.6 a-d**
**a**: R = $C_2H_5$ 80%
**b**: R = $C_4H_9$ 80%
**c**: R = $CH_2C_6H_5$ 71%
**d**: R = $CH_2CH{=}CH_2$ 60%

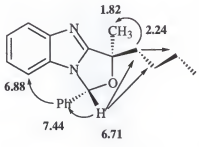
Scheme 5.3

The structures assigned to compounds **5.5a-d** were confirmed by $^1$H- and $^{13}$C-NMR. All compounds present signals characteristic for the 5-methyl group: a singlet in the $^1$H-NMR spectra at about 1.8-1.9 ppm, and a signal at 25-26 ppm in the $^{13}$C-NMR spectra, the latter was unequivocally assigned to a methyl group by "attached proton test" experiments. The $^1$H-NMR spectra of compounds **5.5a-d** all feature the characteristic benzimidazole coupling pattern: *d-t-t-d* with a 8.1-8.4 Hz coupling constant (*ortho*

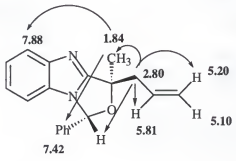
coupling), corresponding to four adjacent aromatic protons (exceptionally for compound **5.5c** the aromatic signals of the benzyl group overlap those of benzimidazole). In the $^{13}C$-NMR spectra, the six benzimidazole ring signals are also well defined, at about 160, 149, 135, 123, 122, 120 and 110 ppm. The chemical shifts of the hydrogen (5.7-6.7 ppm, singlet) and carbon (88 ppm) in the 2-position of the oxazole ring are deshielded, due to the presence of vicinal heteroatoms.




**5.5a**




**5.5b**




**5.5d**

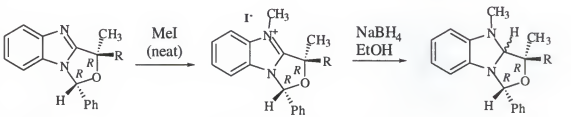
Scheme 5.4. Results of NOE experiments for compounds **5.5a**, **5.5b** and **5.5d**.

The results of NOEDIF experiments for compounds **5.5a**, **5.5b** and **5.5d** are depicted in Scheme 5.4. In compound **5.5a**, irradiating the 2-H induced positive NOE's at the signals characteristic for the 5-ethyl group, while irradiating the signal characteristic for the 2-methyl group caused a positive NOE to be observed at the 5-phenyl group hydrogen atoms.

In compound **5.5b**, irradiating the 2-H induced positive NOE's at the signals characteristic for the 5-butyl group. Interestingly, there is a higher positive NOE on the β-$CH_2$ of the *n*-butyl group than on the α-$CH_2$, which may suggest that the molecule adopts a specific conformation in solution. Irradiating the signal characteristic for the phenyl group caused a positive NOE to be observed at the 5-$CH_3$ hydrogen atoms. In compound **5.5d**, irradiation of the allylic methylene produced a positive NOE at the hydrogen in position 2. In agreement with this, irradiation of the 5-$CH_3$ protons produced a positive NOE on the phenyl ring protons. These experiments confirmed that the alkylation of **5.4** proceeded with retention of configuration at 5-C.

Compounds **5.5a-d** were hydrolyzed under mild acidic conditions ($Et_2O$, 5% HCl) to give enantiomerically pure 2-(α-hydroxyalkyl)-benzimidazoles **5.6a-d**. The enantiomeric purity was determined by measuring the rotation angles of the polarized light: $\alpha_D$ values for compounds **5.5a-d** range between 66° and 94°, while for compounds **5.6a-d** are found between 16.3° and 89.1 °.

1*H*,3*H*-Oxazolo[3,4-*a*]benzimidazole derivatives **5.5b-d** were converted to the benzimidazolium iodides **5.7b-d**, which were reduced, with sodium borohydride, to compounds **5.8b-d** (Scheme 5.5).



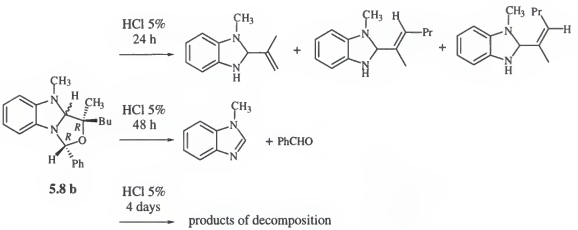

**5.5 b-d**
**b:** R = $C_4H_9$
**c:** R = $CH_2C_6H_5$
**d:** R = $CH_2CH{=}CH_2$

**5.7 b-d**
**b:** R = $C_4H_9$
**c:** R = $CH_2C_6H_5$
**d:** R = $CH_2CH{=}CH_2$

**5.8 b-d**
**b:** R = $C_4H_9$
**c:** R = $CH_2C_6H_5$
**d:** R = $CH_2CH{=}CH_2$

Scheme 5.5

Surprisingly, the hydrolysis of compounds **5.8b-d** under mild acidic conditions as described by Mukaiyama for the cleavage of similar imidazole derivatives [78CL1253, 81T4111], did not afford the expected α-hydroxy aldehydes, but decomposition products (Scheme 5.6), perhaps due to the extended conjugation of the unshared pair of electrons of the nitrogen atom in position 3 with the fused benzene ring.



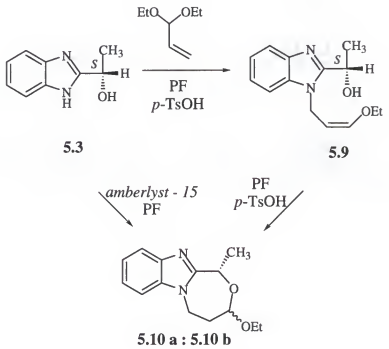

Scheme 5.6

An interesting type of oxazepine derivative **5.10** was obtained when the chiral benzimidazole **5.3** underwent condensation with acrolein diethylacetal under the conditions described above or using an acidic resin as catalyst (Scheme 5.7).

## 5.3 Conclusions

The principle of self-regeneration of stereocenters (SRS), as presented by Seebach [96AG2708] is simple: the chiral starting material, possesing two functional groups and one chiral center (in our case 1-H-benzimidazolyl-ethanol) is allowed to react with an aldehyde to form an acetal. The new chiral compound contains now a second chiral center (with a conformation influenced by the conformation of the first chiral center). subsequent

reaction at the chiral center proceeds diastereoselectively, with inversion of configuration. Cleavage of the acetal unit leads to the final product. In the SRS methodology the initial chiral center is converted to a trigonal geometry and finally regenerated under the influence of the chiral center of the acetal. In our methodology, the geometry of the initial chiral center remains unchanged and the electrophilic attack proceeds without inversion of configuration.




Scheme 5.7

In the present work we have proposed three objectives:

(i) to improve the yield of **5.5a** compared to that previously reported [97TA1491] and obtain a few more examples of 5-substituted 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles;

(ii) to design a new method for the synthesis of (α-hydroxyalkyl)benzimidazoles;

(iii) to obtain α-hydroxy aldehydes via the hydrolysis of 5-substituted 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles.

1*H*,3*H*-Oxazolo[3,4-*a*]benzimidazoles **5.5a-d** were obtained using an improved lithiation method and were converted into 2-(α-hydroxyalkyl)benzimidazoles **5.6a-d** in excellent yields, thus providing an efficient approach to stereoselective synthesis of 2-(α-hydroxyalkyl)benzimidazoles as pure D-enantiomers.

Nevertheless, the hydrolysis of 5-substituted 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles did not afford α-hydroxy aldehydes, even under harsh reaction conditions.

## 5.4 Experimental Section

### General procedure for the synthesis of compounds **5.5a-d**

A solution of 2-phenyl-5-methyl-oxazolo[3,4-*a*]benzimidazole **5.4** (1 equiv) in THF at -78° C under Argon atmosphere was treated with *s*-BuLi (1.1 equiv, 1.3 M in cyclohexane) and TMEDA (1 equiv), under stirring. The resulting suspension was kept at -78°C for 2 h, when the appropriate electrophile (alkyl halide) (1 equiv) was added. The reaction mixture was stirred at -78° C for 2h, and then at r.t. overnight. The reaction was quenched with saturated $NH_4Cl$, extracted with diethyl ether, and the organic layer dried ($Na_2SO_4$). The solvent was removed under vacuum to give the product as a yellow oil. The crude product was purified by column chromatography on silica gel/hexane : ether = 1 : 2.

(1*R*,3*R*)-3-Ethyl-3-methyl-1-phenyloxazolo[3,4-*a*]benzimidazole (**5**, **5a**).

[97TA1491] Yield 85%, m.p. 122-123°C (lit. [97TA1491] 122-124°C), $[\alpha]_D$ = 103.0.

(1*R*,3*R*)-3-Butyl-3-methyl-1-phenyloxazolo[3,4-*a*]benzimidazole (**5**, **5b**).

Yield 80%, m.p. 120-121°C; $[\alpha]_D$ = 78.4° at 25° C (c = 0.01 g/ml, chloroform) $\delta_H$ ($CDCl_3$): 7.78 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 5H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.70 (s, 1H), 2.07-2.02 (m, 2H), 1.83 (s, 3H), 1.59-1.57 (m, 1H), 1.37-1.22 (m, 3H), 0.88 (t, *J* = 6.0 Hz, 3H); $\delta_C$ ($CDCl_3$): 161.5, 149.2, 136.1, 130.3, 130.0, 129.0, 127.1, 122.4, 122.4, 120.1, 110.0, 88.4, 82.2, 39.9, 26.0, 25.9, 22.7, 13.8. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.08; H, 7.36; N, 9.16.

(1*R*,3*R*)-3-Benzyl-3-methyl-1-phenyloxazolo[3,4-*a*]benzimidazole (**5**, **5c**).

Yield 78%, oil; $[\alpha]_D$ = 94.1° at 25° C (c = 0.01 g/ml, chloroform) $\delta_H$ ($CDCl_3$): 7.78 (d, *J* = 8.4 Hz, 1H), 7.39-6.98 (m, 12H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.74 (s, 1H), 3.44 (d, *J* = 13.8 Hz, 1H), 3.25 (d, *J* = 13.8 Hz, 1H), 1.91 (s, 3H); $\delta_C$($CDCl_3$): 160.5, 149.1, 135.6, 135.4, 130.2, 130.1, 129.8, 128.8, 127.9, 127.6, 127.0, 126.8, 122.2, 120.0, 109.7, 88.4, 82.3, 46.1, 26.3. HRMS (POS FAB NBA) m/e 341.1659 (M+1). Calcd. for $C_{23}H_{20}N_2O + H^+$: 341.1653.

(1*R*,3*R*)-3-Allyl-3-methyl-1-phenyloxazolo[3,4-*a*]benzimidazole (**5.5d**)

Yield 79%, oil; $[\alpha]_D$ = 66.7 ° at 25° C (c = 0.01 g/ml, chloroform) $\delta_H$ ($CDCl_3$): 7.76 (d, *J* = 8.4 Hz, 1H), 7.42 (m, 5H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 5.87-5.75 (m, 1H), 5.20 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 2.81-2.72 (m, 2H), 1.83(s, 3H); $\delta_C$($CDCl_3$): 161.0, 149.3, 135.9, 131.8, 130.4, 130.1, 129.0, 127.1, 122.5, 122.4, 120.2, 119.9, 110.0, 88.5, 81.6, 44.2, 25.7. For $C_{19}H_{18}N_2O$: Anal. Calcd: H, 6.25; N, 9.65. Found: H, 6.50; N, 9.88.

General procedure for the synthesis of 2-(α-Hydroxyalkyl)benzimidazoles **5.6a-d**

A solution of compound ***5.5*** (4 mmol) in ether was treated with an excess of HCl sol. 5% and the reaction mixture stirred for 2 days at r.t. The mixture was extracted with chloroform (2 × 100ml), the aqueous layer was neutralized with aq. $NaHCO_3$ 5% and extracted with chloroform (2 × 50ml). This second organic layer was dried ($Na_2SO_4$) and evaporated under vacuum to give a white solid.

(2*R*)-2-(1*H*-Benzo[*d*]imidazo-2-yl)-1-butan-2-ol (**5.6a**).

Yield 78%, m.p. 170-172°C; $[\alpha]_D$ = 16.3° at 25° C (c = 0.01 g/ml, methanol) $\delta_H$ (DMSO): 7.49-7.47 (m, 2H), 7.12-7.09 (m, 2H), 5.44 (s, 1H), 3.37 (br s, 1H), 1.88-1.83 (m, 2H), 1.54 (s, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); $\delta_C$ (DMSO): 160.5, 125.6, 123.0, 121.1, 121.0, 120.9, 112.8, 71.6, 35.2, 27.8, 8.3. Anal. Calcd for $C_{11}H_{14}N_2O$: N, 14.72. Found: N, 14.82.

(2*R*)-2-(1*H*-Benzo[*d*]imidazo-2-yl)-1-hexan-2-ol (**5.6b**).

Yield 80%, m.p. 158-160° C; $[\alpha]_D$ = 22.8° at 25°C (c = 0.01 g/ml, methanol) $\delta_H$ (DMSO): 12.07 (br s, 1H), 7.48 (s, 2H), 7.12-7.09 (m, 2H), 5.45 (s, 1H), 1.91-1.74 (m, 2H), 1.56 (s, 3H), 1.40-1.00 (m, 4H), 0.80 (t, *J* = 6.9 Hz, 3H); $\delta_C$ (DMSO): 160.6, 120.8, 114.0, 112.9, 71.2, 42.3, 28.1, 25.6, 22.3, 13.8 (the benzimidazole signals are not always observable). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.34; H, 8.49; N, 12.92.

(2*R*)-2-(1*H*-Benzo[*d*]imidazo-2-yl)-1-phenylpropan-2-ol (**5.6c**).

Yield 71%, m.p. 207-208°C; $[\alpha]_D$ = 80.4° at 25° C (c = 0.01 g/ml, methanol) $\delta_H$ (DMSO): 12.07 (s (br), 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.14-7.05 (m, 7H), 5.71 (s, 1H), 3.19 (q, *J* = 13.2 Hz, 2H), 1.54 (s, 3H); $\delta_C$ (DMSO): 160.5, 143.2, 137.4, 134.1, 130.4, 127.6, 126.1, 121.5, 120.9, 118.4, 111.4, 71.9, 48.1, 27.9. Anal. Calcd for $C_{16}H_{16}N_2O$: H, 6.39; N, 11.10 Found: H, 6.35; N, 11.03.

(2*R*)-2-(1*H*-Benzo[*d*]imidazo-2-yl)-4-penten-2-ol (**5.6d**).

Yield 60%, m.p. 165-167°C; $[\alpha]_D$ = 89.1° at 25° C (c = 0.01 g/ml, methanol) $\delta_H$ (DMSO): 12.13 (br s, 1H), 7.56-7.53 (m, 1H), 7.44-7.41 (m, 1H), 7.15-7.07 (m, 2H), 5.82-5.71 (m, 1H), 5.63 (s, 1H), 5.03-4.96 (m, 2H). 2.62 (d, *J* = 6.9 Hz, 2H), 1.55 (s, 3H); $\delta_C$ (DMSO): 160.3, 143.1, 134.2, 134.2, 121.4, 120.8, 118.4, 117.6, 111.3, 71.1, 46.8, 27.6. For $C_{12}H_{14}N_2O$: Anal. Calcd: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.89; H, 7.00; N, 13.90.

General procedure for the synthesis of compounds **5.7b-d**

A solution of 2-phenyl-5-alkyl-5-methyl-oxazolo[3,4-*a*]benzimidazole **5.5b-d** (1 equiv) was stirred in excess of MeI (10 equiv), until no more starting material was observed (by GC). The excess MeI was evaporated under vacuum to give a yellow oil.

(1*R*,3*R*)-3-Butyl-3,4-dimethyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazol-4-ium iodide **5.7b**.

Yield 93%, oil; $[\alpha]_D$ = 12.0° at 25° C (c = 0.01 g/ml, chloroform), mixture of diastereomers A : B = 1 : 1.5 $\delta_H$ ($CDCl_3$): 8.00-7.93 (m, 2H, A+B), 7.75-7.37 (m, 16H, A+B), 7.09 (d, *J* = 8.4 Hz, 1H, A), 7.01 (d, *J* = 8.4 Hz, 1H, B), 4.32 (s, 6H, A+B), 2.45-2.02 (m, 10H, A+B), 1.70-1.61 (m, 2H, A+B), 1.48-1.23 (m, 6H, A+B), 0.95-0.90 (m, 6H, A+B); $\delta_C$ ($CDCl_3$): 156.2 (A), 156.0 (B), 137.4 (B), 137.3 (A), 131.8 (A), 131.8 (B), 131.4 (A), 131.4 (B), 129.3(A), 129.1 (B), 129.1 (A), 128.6 (B), 127.8 (B), 127.8 (A), 127.1 (B), 127.0 (A), 126.3 (A), 125.8 (B), 114.2 (B), 114.1 (A), 113.1 (A), 113.0 (B), 91.3 (B), 90.7 (A), 84.5 (B), 84.4 (A), 37.8 (B), 37.3(A), 33.8 (B), 33.2(A), 25.9 (A), 25.5 (B), 24.1 (A), 24.1 (A), 22.1 (B), 22.0 (A), 13.6 (B), 13.5 (A) (the benzimidazole signals are not always observable). HRMS (POS FAB NBA) m/e 321.1967 (M-I). Calcd. for $C_{21}H_{25}N_2O^+$ 321.1967.

(1*R*,3*R*)-3-Benzyl-3,4-dimethyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazol-4-ium iodide **5.7c**.

Yield 96%, oil; $[\alpha]_D$ = 27.8° at 25°C (c=0.01 g/ml, chloroform), mixture of diastereomers A : B = 1 : 2; $\delta_H$ ($CDCl_3$): 8.11 (d, *J* = 7.8 Hz, 1H, A), 7.87 (d, *J* = 8.7 Hz, 1H, A), 7.84 (d, *J* = 8.7 Hz, 1H, B), 7.63 (d, *J* = 6.9 Hz, 1H, B), 7.59-7.00 (m, 12H, A+B), 6.91 (d, *J* = 8.4 Hz, 1H, B), 6.84 (d, *J* = 8.3 Hz, 1H, A), 4.38 (s, 3H, A),

4.00 (s, 3H, B), 3.69 (s, 2H, B), 3.61 (s, 2H, A), 2.17 (s, 3H, B), 2.14 (s, 3H, A); $\delta_C$ ($CDCl_3$): 155.7 (A), 155.2 (B), 137.3 (A), 137.2 (B), 133.3 (A), 133.1 (B), 131.6 (B), 131.5 (A), 131.5 (B), 131.3 (A), 130.2 (A), 130.2 (B), 129.2 (B), 128.9 (A), 128.8 (B), 128.6 (A), 128.0 (A), 128.0 (B), 127.9 (A), 127.9 (B), 127.5 (A), 127.4 (A), 127.2 (B), 127.1 (B), 126.3 (A), 125.8 (B), 116.1 (A), 114.1 (B), 113.1 (A), 112.9 (B), 91.4 (B), 91.1 (A), 85.1 (2C, A+B), 44.5 (B), 44.2 (A), 34.7 (A), 34.0 (B), 24.8 (A), 24.1 (B). Anal. Calcd for $C_{24}H_{23}N_2OI$: H, 4.81; N, 5.81. Found: H, 5.00; N, 5.42.

(1*R*,3*R*)-3-Allyl-3,4-dimethyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazol-4-ium iodide **5.7d.**

Yield 96%, oil; $[\alpha]_D$ = 7.1° at 25°C (c=0.01 g/ml, chloroform), mixture of diastereoisomers A : B = 3 : 1, $\delta_H$ ($CDCl_3$): 7.90 (d, 1H, *J* = 8.4 Hz, A), 7.89 (d, 1H, *J* = 11.0 Hz, B), 7.74 (d, 1H, *J* = Hz, A), 7.68 (d, 1H, J = Hz, B), 7.62-7.35 (m, 7H, A+B), 7.06 (d, *J* = 8.4 Hz, 1H, A), 7.00 (d, *J* = 8.4 Hz, 1H, B), 6.00-5.89 (m, 1H, A+B), 5.45-5.38 (m, 1H, A+B), 5.31-5.25 (m, 1H, A+B), 4.31 (s, 3H, A), 4.27 (s, 3H, B), 3.25-3.06 (m, 2H, A+B), 2.14 (s, 3H, A), 2.12 (s, 3H, B); $\delta_C$ ($CDCl_3$): 155.4(A), 155.4(B), 137.4(A+B), 131.7(A), 131.4(A+B), 131.2(B), 129.9(B), 129.5(A), 129.3(B), 129.2(A), 128.7(B), 127.9(2C, A+B), 127.1(A), 127.1(B), 125.9(A), 122.4(A), 121.4(B), 114.1(A), 114.0(B), 113.1(B), 113.0(A), 91.4(A), 90.8(B), 84.6(B), 84.4(A), 42.7(A), 42.0(B), 34.5(A), 34.2(B), 24.2(B), 24.1(A). HRMS (POS FAB NBA) m/e 305.1653 (M-I$^+$). Calcd. for $C_{20}H_{21}N_2O^+$ 305.1653.

General procedure for the synthesis of compounds **5.8 b-d**

A solution of 2-phenyl-5-alkyl-5-methyl-oxazolo[3,4-*a*]benzimidazole **5.5b-d** (1 equiv) was stirred in excess of MeI (10 equiv), until no more starting material was observed (by GC). The excess MeI was evaporated under vacuum and the resulting yellow oil was dissolved in 20 ml of MeOH at 0°C. To the stirred solution $NaBH_4$ (10 equiv) was added portionwise, and the reaction mixture was refluxed for 18 h. The solvent was evaporated under vacuum, and the residue dissolved in methylene chloride (50 ml). The organic layer was washed with water (2 × 30ml), dried ($Na_2SO_4$), and the solvent evaporated. Purification by flash chromatography (silica gel/hexane : ether = 1 : 2) gave the product as a yellow oil.

(1*R*,3*R*)-3-Butyl-3,4-dimethyl-1-phenyl-3*a*,4-dihydro-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole **5.8b**.

Yield 84%, oil; $[\alpha]_D$ = 6.02° at 25° C (c = 0.01 g/ml, chloroform), mixture of diastereoisomers A : B = 1 : 1, $\delta_H$ ($CDCl_3$): 7.55 (d, *J* = 6.9 Hz, 2H, A+B), 7.40-7.30 (m, 3H, A+B), 6.78 (t, *J* = 6.0 Hz, 1H, A), 6.75 (t, *J* = 6.0 Hz, 1H, B), 6.52 (t, *J* = 6.0 Hz, 1H, A), 6.50 (t, *J* = 6.0 Hz, 1H, B), 6.39-6.29 (m, 2H), 5.55 (s, 1H, A), 5.49 (s, 1H, B), 4.91 (s,1H, A), 4.86 (s, 1H, B), 2.83 (s, 3H, A+B), 2.76-1.17 (m, 9H, A+B), 0.95-0.84 (m, 3H, A+B); $\delta_C$($CDCl_3$): 145.7(B), 145.7(A), 140.8(B), 140.6(A), 128.7(A), 128.6(B), 128.4(A), 128.3(B), 127.1(A), 127.0(B), 122.3(B), 122.0(A), 118.2(A), 118.0(B), 110.9(B), 110.2(A), 105.7(A), 105.2(B), 95.1(A), 94.8(B), 94.7(A), 93.0(B), 85.0(A), 84.4(B), 39.7 (1C, A+B), 34.8(A), 34.5(B), 31.5(A),

31.2(B), 25.9(A), 25.0(B), 23.3(A), 23.2(B), 18.1(1C, A+B), 14.0(A), 13.9(B). For $C_{21}H_{26}N_2O$: Anal. Calcd: H, 8.13; N, 8.69 Found: H, 7.91; N, 8.55.

(1*R*,3*R*)-3-Benzyl-3,4-dimethyl-1-phenyl-3*a*,4-dihydro-3*H*-[1,3]oxazolo[3,4-*a*] benzimidazole **5.8c.**

Yield 88%, oil, mixture of diastereomers A : B = 5 : 1; $[\alpha]_D$ = 118.5° at 30° C $\delta_H$ ($CDCl_3$): 7.87 (d, *J* = 6.9 Hz, 1H, A), 7.64-7.15 (m, 9H, A), 7.64-7.15 (m, 10H, B), 6.80 (t, *J* = 6.0 Hz, 1H, A), 6.78 (t, *J* = 6.0 Hz, 1H, B), 6.57 (t, *J* = 6.0 Hz, 1H, A), 6.54 (t, *J* = 6.0 Hz, 1H, B), 6.42 (t, *J* = 8.7 Hz, 2H, A+B), 5.83 (s, 1H, A), 5.56 (s, 1H, B), 5.04 (s, 1H, A), 5.00 (s, 1H, B), 3.00 (d, *J* = 14.4 Hz, 1H, B), 2.94, (d, *J* = 19.2 Hz, 1H. A), 2.94 (s, 3H, A+B), 2.61 (d, *J* = 19.2 Hz, 1H, A), 2.55 (d, *J* = 14.4 Hz, 1H, B), 1.27 (s, 3H, A+B) ; $\delta_C$ ($CDCl_3$): 145.6 (2C, A+B), 140.7 (1C, A+B), 140.5 (1C, A+B), 137.1 (A), 139.4 (B), 130.8 (B), 130.5 (A), 128.9 (B), 128.8 (A), 128.5 (A), 128.4 (B), 128.1 (B), 127.9 (A), 127.3 (B), 127.0 (A), 126.7 (B), 126.2 (A), 122.4 (B), 122.2 (A), 118.4 (A), 118.2 (B), 110.8 (B), 110.3 (A), 105.7 (A), 105.7 (B), 95.1 (B), 95.0 (A), 94.9 (A), 91.6 (B), 84.9 (B), 84.3 (A), 46.0 (B), 37.4 (A), 35.1 (A), 31.6 (B), 23.3 (A), 22.6 (B) .For $C_{24}H_{24}N_2O$: Anal. Calcd: H, 6.79; N, 7.86. Found: H, 6.70; N, 5.42.

(1*R*,3*R*)-3-Allyl-3,4-dimethyl-1-phenyl-3*a*,4-dihydro-3*H*-[1,3]oxazolo[3,4-*a*] benzimidazole **5.8d.**

Yield 85%, oil, mixture of diastereomers A : B = 2 : 1; $[\alpha]_D$=23.6° at 30° C $\delta_H$ ($CDCl_3$): 7.54 (d, *J* = 7.8 Hz, 2H, A+B), 7.39-7.23 (m, 3H, A+B), 6.79-6.73 (m, 1H, A+B), 6.53 (d, *J* = 7.5 Hz, 1H, A), 6.50 (d, *J* = 7.5 Hz, 1H, B), 6.38-6.32 (m, 2H, A+B), 5.95-5.83 (m, 1H, A+B), 5.85 (s, 1H, A), 5.57 (s, 1H, B), 5.16-5.01 (m, 2H, A+B), 4.92 (s, 1H, A), 4.90 (s, 1H, B), 2.82 (s, 3H, A), 2.79 (s, 3H, B), 2.46-2.37 (m,

2H, A), 2.11-2.04 (m, 2H, B), 1.36 (s, 3H, A), 1.17 (s, 3H, B); $\delta_C$ ($CDCl_3$): 145.4 (1C, A+B), 140.5 (1C, A+B), 133.2 (B), 133.0 (A), 128.7 (A), 128.6 (B), 128.4 (A), 128.3 (B), 128.2 (B), 127.9 (A), 127.1 (B), 126.9 (A), 122.4 (B), 122.1 (A), 118.5 (B), 118.2 (A), 118.2 (A), 117.8 (B), 110.9 (B), 110.1 (A), 105.8 (B), 105.4 (A), 95.0 (A), 94.9 (B), 94.1 (A), 92.0 (B), 84.2 (B), 83.7 (A), 44.3 (A). 36.5 (B), 34.8 (B), 34.7 (A), 23.2 (A), 18.5 (B). For $C_{20}H_{22}N_2O$: Anal. Calcd: H, 7.24; N, 9.14. Found: H, 7.18; N, 8.73.

Synthesis of (1*R*)-1-{1-[(*Z*)-3-ethoxy-2-propenyl]-1H-benzo[*d*] imidazo-2-yl}ethan-1-ol **5.9**.

1*H*-Benzimidazole-2-methanol (1 equiv) and acrolein dimethyl acetal (1.1 equiv) were refluxed in perfluorocarbon fluid for 24 h under catalytic conditions using a reverse Dean-Stark. The reaction was monitored by GC. After completion the reaction mixture was allowed to reach r.t., the solvent was separated and the product was separated by column chromatography (silica gel, hexane : ether = 1 : 2). Yield 70%. $\delta_H$ ($CDCl_3$): 7.77-7.67 (m, 1H), 7.28-7.24 (m, 3H), 6.55 (d, $J$ = 6.6 Hz, 1H), 5.12 (q, $J$ = 6.0 Hz, 1H), 4.91-4.82(m, 1H), 4.72 (d, $J$ = 6.0 Hz, 2H), 4.38-4.31 and 4.08-4.01 (dm, 1H), 3.65 (q, $J$ = 6.9 Hz, 2H), 1.67 (d, $J$ = 6.0 Hz, 3H), 1.20 (t, $J$ = 6.0Hz, 3H); $\delta_C$ ($CDCl_3$): 156.1, 149.6, 147.5, 141.3, 135.0, 122.8, 122.3, 109.8, 98.0, 64.6, 63.2, 42.4, 22.1, 14.3. For $C_{14}H_{18}N_2O_2$: Anal. Calcd: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.21; H, 7.73; N, 11.15.

Synthesis of (1*R*, 3*R*)-3-ethoxy-1-methyl-4,5-dihydro-1*H*,3*H*-benzo[4,5]imidazo [2,1-c][1,4]oxazepine **5.10a** and (1*R*,3*S*)-3-ethoxy-1-methyl-4,5-dihydro-1*H*,3*H*-benzo [4,5]imidazo[2,1-c][1,4]oxazepine **5.10b**

(1*R*)-1-{1-[(*Z*)-3-Ethoxy-2-propenyl]-1*H*-benzo[*d*] imidazo-2-yl}ethan-1-ol **5.9**

(1 equiv) was refluxed in perfluorocarbon fluid for 24 h under catalytic conditions (*p*-TsOH), using a reverse Dean-Stark. The reaction was monitored by GC. After completion the reaction mixture was allowed to reach r.t., the solvent was separated and the product was separated by column chromatography (silica gel, hexane : ether = 1 : 2). Compound **5.10b** was separated as the first fraction (yield 45%) and compound **5.10a** as the second fraction (yield 35%).

**5.10a** $\delta_H$ ($CDCl_3$): 7.77 (d, *J* = 6.0 Hz, 1H), 7.34-7.22 (m, 3H), 4.88-4.78 (m, 2H), 4.51-4.44 (m, 1H), 4.11-3.96 (m, 2H), 3.56-3.54 (m, 1H), 2.35-2.27 (m, 1H), 2.09-2.00 (m, 1H), 1.87 (d, *J* = 6.0 Hz, 3H), 1.27 (s, 3H); $\delta_C$ ($CDCl_3$): 155.9, 141.7, 135.3, 122.5, 121.8, 119.8, 108.7, 104.8, 68.5, 64.1, 39.4, 34.8, 18.8, 14.9.

**5.10b** $\delta_H$ ($CDCl_3$): 7.78-7.74 (m, 1H), 7.28-7.19 (m, 3H), 5.29 (q, *J* = 9.0 Hz. 1H), 4.34-4.26 (m, 1H), 4.08-4.00 (m, 1H), 3.94-3.84 (m, 1H), 3.65-3.55 (m, 1H), 2.22 (q, *J* = 6.0 Hz, 2H), 1.80 (d, *J* = 6.0 Hz, 3H), 1.29 (t, *J* = 6.0Hz, 3H); $\delta_C$ ($CDCl_3$): 155.9, 141.7, 135.3, 122.5, 121.8, 119.8, 108.7, 104.8, 68.5, 64.1, 39.4, 34.8, 18.8, 14.9. For $C_{14}H_{18}N_2O_2$: Anal. Calcd: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.26; H, 7.53; N, 11.28.

# CHAPTER 6

# ALKYLATION OF BENZOTRIAZOL-1-YL ALKYL AND ARYL SULFOXIDES

## 6.1 Introduction

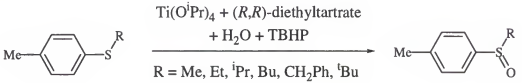
A wide range of natural or synthetic biologically active compounds contain a sulfoxide functional group. Due to the tetrahedral geometry of sulfur, sulfoxides can be chiral and often only one enantiomer is responsible for the desired biological activity.

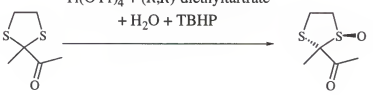
The existence of several efficient methods to obtain homochiral sulfoxides, as well as their synthetic capabilities has led to the development of new applications of chiral sulfoxides in asymmetric synthesis. The enantiomerically pure sulfinyl group has been used successfully to control the stereochemistry of the product in the key step of total syntheses of biologically active compounds. A few examples are: asymmetric reductions of β-keto sulfoxides [95MI1], Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides [95MI1], C-C bond formation using sulfoxide-stabilized carbanions [71JACS3077, 77TL4009, 84TL4113, 87JCS(P1)781, 89JOC2663, 95CR1717] or Diels-Alder reactions of vinyl sulfoxides [95MI1].

6.1.1 Synthesis of Homochiral Sulfoxides

6.1.1.2 Asymmetric Oxidation of Thioethers

Several methods are available for the preparation of optically active sulfoxides: optical resolution, asymmetric oxidation and asymmetric synthesis. The first efficient asymmetric oxidation of sulfides to sulfoxides was reported by Kagan [84TL1049] who used a modification of the Sharpless reagent. The well-known Sharpless epoxidation of allylic alcohols uses one mole equiv. of titanium isopropoxide per mole of L-diethyl tartrate under anhydrous conditions and gives the desired epoxide in excellent enantiomeric purity. In the case of sulfoxides, Sharpless reagent is not enantioselective unless the DET/titanium ratio is decreased, or one equiv. of water is added. The method has been applied intensively in numerous asymmetric syntheses of chiral sulfoxides with up to 93% e.e. (Scheme 6.1) [95TL6537, 96TL8929, 97TL5047]. The sulfoxides of cyclic dithioacetals are used for stereoselective syntheses (e.g. α-hydroxyketone derivatives) due to their reduced conformational mobility; the acyl group provides a useful functionality for further elaboration.

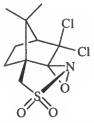



Scheme 6.1

Other enantioselective reagents for the oxidation of prochiral sulfides are several chiral oxaziridines like (+)-8,8-dichlorocamphorylsulphonyl oxaziridine (Scheme 6.2), now

commercially available. These oxaziridines gave excellent enantioselectivity: 88-92% e.e [94CI636].

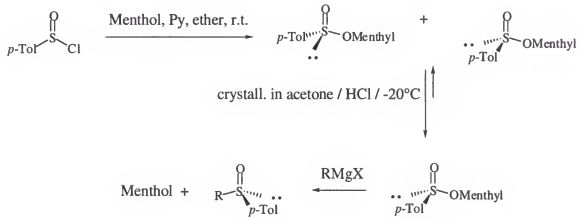


(+)-8,8-dichlorocamphorylsulphonyl oxaziridine

Scheme 6.2

6.1.1.2 Nucleophilic Substitution in Chiral Sulfur Derivatives

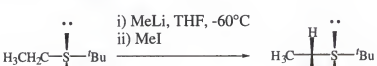
The most common approach is the Andersen synthesis (Scheme 6.3) based on the nucleophilic substitution of menthoxy group in diastereomerically pure (S,S)-menthyl *p*-toluenesulfinate with Grignard reagents which occurs with full inversion of configuration at sulfur. This method has been used to prepare *p*-tolyl alkyl or aryl sulfoxides [95CR1717].



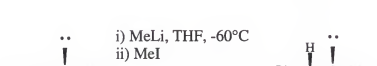

Scheme 6.3

6.1.2 Stereochemical Behavior of α–Lithio Sulfoxides

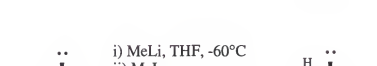
In 1971 Durst reported that the lithium carbanion of $S_R$-*tert*-butyl phenylmethyl sulfoxide underwent highly diastereoselective reactions with $D_2O$, MeI and acetone [71JACS3077]. By replacing the *t*-Bu group with methyl the diastereomeric ratios decreased drastically as shown below (Scheme 6.4).




9 : 1



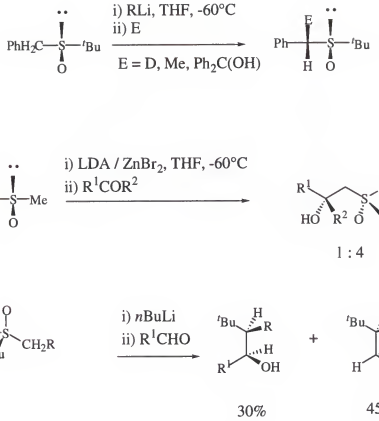

15 : 1




99 : 1

Scheme 6.4

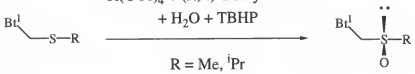
The addition of simple α-sulfinyl carbanions to aldehydes and ketones takes place with poor diastereoselectivity [95CR1717]. The stereochemical outcome of the process was shown to be highly independent on the nature of the sulfoxide and the carbonyl derivative, the diastereoselectivity was thought to be enhanced by the use of $Zn^{+2}$ as metal counterion (Scheme 6.5) [77TL4009, 84TL4113, 89JOC2663]. Again only *tert*-Bu or aryl (*p*-tolyl, *o*-naphtyl) sulfoxides showed diastereoselectivity in this reaction.



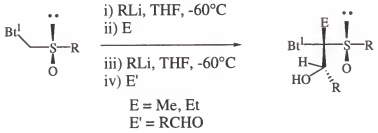

Scheme 6.5

6.1.3 Stereochemical Behavior of α-Lithio-α-benzotriazol-1-ylmethyl Alkyl Sulfoxides

Given the wide range of synthetic methods using chiral sulfoxides, we decided to investigate the stereochemical outcome of lithiation-alkylation reactions of α-benzotriazol-1-ylmethyl alkyl sulfoxides. These compounds have the advantage of the presence of benzotriazol-1-yl group in the α-position, that can be displaced *via* nucleophilic substitution or undergo other synthetic transformations. Our intial strategy was to explore whether the presence of the chiral sulfoxide group can influence the e.e. of a third chiral center (Schemes 6.6 and 6.7). The asymmetric oxidation of the sulfide could be carried out using the modified Sharpless reagent. Subsequently an alkyl group would be introduced at the $C_\alpha$ to the benzotriazole, followed by reaction of the lithiated derivative with an aldehyde.




Scheme 6.6

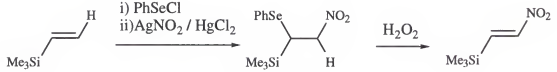



Scheme 6.7

6.1.4. *Trans*-1-benzotriazol-1-yl-2-(trimethylsilyl)ethylenes- Equivalents of Acetylene and Monosubstituted Acetylenes

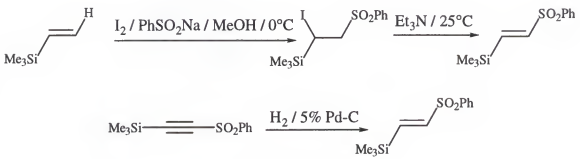
The well-known explosive nature and low dienophilic reactivity of acetylene led to the development of a great number of acetylene equivalents. Among these *trans*-1-benzenesulfonyl-2-(trimethylsilyl)ethylene and trimethyl(2-nitro-1-ethenyl)silane proved their efficiency in Diels-Alder reactions. Both compounds are obtained in multi-step syntheses involving not readily available and extremely toxic starting materials:

- nitroselenenylation of vinylsilanes, which involves treatment with benzeneselenenyl halides followed by addition of silver nitrite in the presence of mercury (II) chloride gave nitroselenides; subsequent oxidation of these derivatives with $H_2O_2$ led to trimethyl(2-nitro-1-ethenyl)silanes [84JOC3235];




Scheme 6.8

- *trans*-1-benzenesulfonyl-2-(trimethylsilyl)ethylene is accessible by free radical addition of benzenesulfonyl chloride to trimethylvinylsilane and subsequent dehydrochlorination with triethylamine or by hydrogenation of its acetylenic precursor at 50 psi [81TL4643,97SC1111].




Scheme 6.9

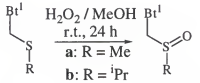
These acetylene equivalents reportedly underwent facile fluoride-induced elimination of β-silylsulfones [79TL2649] to form terminal olefins or Diels-Alder reactions with various dienes (cyclopentadiene, isoprene, cyclohexadiene) [81TL4643, 84JOC3235, 84T2585, 94JCS(CC)1739].

We now report a facile synthesis of an acetylene equivalent: *trans*-1-benzotriazol-1-yl-2-(trimethylsilyl)ethylene from benzotriazol-1-ylmethyl phenyl sulfide via an alkylation with chloromethyltrimethylsilane followed by an oxidation by $NaIO_4$. Alkylation of the product is straightforward, yielding the substituted derivative. The first experiments toward fluoride-induced eliminations and Diels-Alder reactions with cyclopentadiene are also described.

## 6.2 Results and Discussion

### 6.2.1 Non-stereoselective Oxidation of α-Benzotriazol-1-ylmethyl Alkyl Sulfides

The first experiments were carried out using a racemic sulfoxide readily available *via* the non-stereoselective oxidative methods using hydrogen peroxide/methanol (Scheme 6.7) [80BCS5288, 81SC1025]. The reactions proceeded with 85-93% yield.

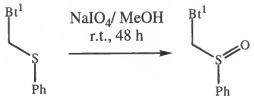



**6.1a,b** **6.2a,b**

Scheme 6.10

### 6.2.2 Non-Stereoselective Oxidation of α-Benzotriazol-1-ylmethyl Phenyl Sulfide

The attempted oxidation of α-benzotriazol-1-ylmethyl phenyl sulfide using the peroxide/methanol system afforded either the starting material (r.t., 24 h) or the corresponding sulfone **6.5** (50 ° C, 24 h). By the use of the $NaIO_4$/methanol system [87JCS(P1)781] at r.t. for 24 h a mixture of sulfoxide : sulfide = 2 : 1 was obtained. Increasing the reaction time to 48 h gave the sulfoxide in 86%. The product was recrystallized from methanol (Scheme 6.11).




**6.3** **6.4**

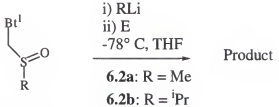
Scheme 6.11

6.2.3 Stereoselective Oxidation of α-Benzotriazol-1-ylmethyl Phenyl Sulfide

The stereoselective oxidation of α-benzotriazol-1-ylmethyl phenyl sulfide using the modified Sharpless reagent was attempted under the conditions described by Kagan (-20 °C for 4 h, followed by warming up to r.t. for 1 h) [84TL1049]. The resulted mixture contained sulfide / sulfoxide in a 3 : 1 ratio. The result can be optimized by monitoring the reaction progress and by increasing the reaction time.

6.2.4 Alkylation of α-Benzotriazol-1-ylmethyl Alkyl Sulfoxides

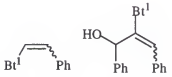
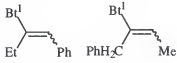
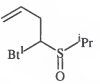
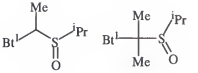
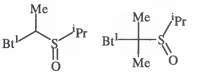
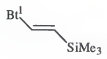
The results of the lithiation / alkylation experiments are summarized below. The diasteromeric mixtures were characterized by GC and NMR spectra of the crude products.




**6.2a**, **b**
**6.4**

Scheme 6.12

Table 6.1 Alkylation experiments using the *n*-BuLi / electrophile sequence.

| Substrate | RLi / E | Product | Comments |
|---|---|---|---|
| **6.2a** | *n*BuLi / EtI |  | 1:1 diastereomers |
| **6.2a** | *n*BuLi / cyclohexanone | S.M. | no reaction |
| **6.2a** | *n*BuLi / $ZnBr_2$ / PhCHO | S.M. | no reaction |
| **6.2a** | LDA / PhCHO | S.M. | no reaction |
| **6.2b** | *n*BuLi / EtI |  | 1 : 1 diastereomers |
| **6.2b** | *n*BuLi / PhCHO |  | from GC-MS |
| **6.2a** | i) *n*BuLi / EtI<br>ii) LDA / $PhCH_2Br$ |  | from GC-MS |
| **6.2b** | i) *n*BuLi / EtI<br>ii) *n*BuLi / BuI |  | one-pot rxn<br>1 : 3.5<br>NMR results |
| **6.2b** | *n*BuLi / PhCOPh | S.M. | no reaction |
| **6.2a** | *n*BuLi / allyl bromide |  | 1 : 1 |
| **6.2b** | i) *n*BuLi / MeI<br>ii) *n*BuLi / PhCHO |  | one-pot rxn |
| **6.2b** | i) *n*BuLi / MeI<br>ii) *n*BuLi / cyclohexanone |  | one-pot rxn |
| **6.4** | *n*BuLi / $ICH_2SiMe_3$ |  | one isomer **6.9** |

The d.e. is quite low when R = Me, $^{i}$Pr and the 2 step reactions are preferable to the one-pot experiments. Similar experiments (Table 6.2) were carried out using the Barbier method of alkylation (Scheme 6.13), when the lithiation is performed in the presence of the electrophile.


**6.2a, b**
**6.4**

i) E
ii) LDA
-78° C, THF

Product

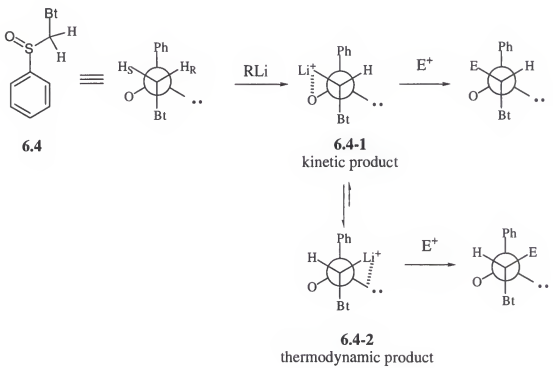
**6.2a**: R = Me
**6.2b**: R = $^{i}$Pr
**6.4**: R = Ph

Scheme 6.13

Table 6.2 Alkylation experiments using the electrophile / LDA sequence

| Substrate | E | | Product | Comments |
|---|---|---|---|---|
| **6.2.a** | MeI | **6.6a** |  | mixture of diastereomers 1 : 1 |
| **6.2.a** | allyl bromide | **6.6b** |  | mixture of diastereomers 1 : 1.7 |
| **6.2.b** | MeI | **6.6c** |  | mixture of diastereomers (NMR only one observable) 1 : 10 |
| **6.4** | MeI | **6.7a** |  | one diastereomer |
| **6.4** | BuI | **6.7b** |  | mixture of diastereomers 1 : 2 |

From these experiments it can be inferred that the stereochemistry of the reaction products depends on the α–sulfinyl carbanions by three factors: (i) kinetic acidity, which controls the stereochemistry of the carbanion initially formed; ii) thermodynamic acidity, which defines the stereochemistry or the conformation of the intermediate carbanion; (iii) reactivity of the carbanion, which may be important to control the stereochemistry of the products. When R = Me the reaction is not diastereoselective, independent of the lithiation method. For R = $^{i}$Pr, using the same electrophile (MeI), the diastereoselectivity increases up to 80% when E = Me, while for R = Ph d.e. >95% (Table 6.2, see **6.6a**, **6.6c** and **6.7a**). As shown by Ohno [87JOC1414] in THF, the countercation of a base employed to abstract a proton from the sulfoxide would initially be trapped by the sulfinyl oxygen (Scheme 6.11). Therefore the $H_S$ in **6.4** is will be abstracted first, being more reactive than $H_R$.



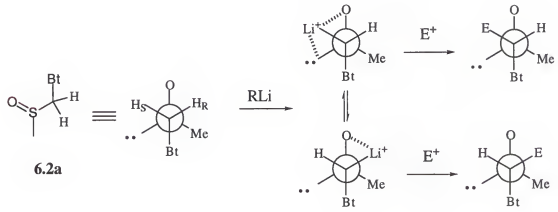

**6.4**

**6.4-1**
kinetic product

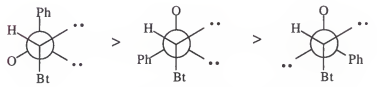
**6.4-2**
thermodynamic product

Scheme 6.14

The $H_S$ and $H_R$ in **6.2a** are similar in reactivity with respect to the distance from the oxygen, and the reaction will give a 1 : 1 diastereomeric mixture (Scheme 6.15). When the lithiation step precedes the addition of electrophile, for **6.4** the resulting anion **6.4-1** will equilibrate with the more stable form **6.4-2** (as shown by Nishio [72TL4839] Scheme 6.16) before the electrophilic attack, while an α-sulfinyl carbanion **6.4-1** formed in the presence of the electrophile will immediately react without affecting the chiral center.




Scheme 6.15



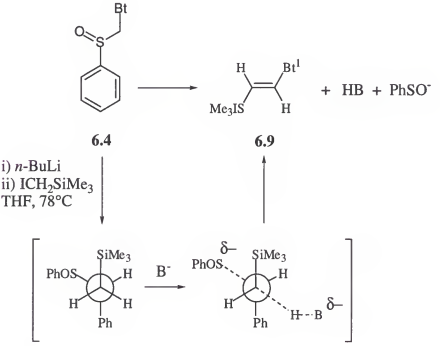

order of stability [72 TL4839]

Scheme 6.16

The nature of the electrophile will influence the diastereoselectivity of the reaction of the same substrate (see **6.7a** and **b**) depending on its reactivity (MeI vs. BuI).

6.2.5. Synthesis of 1-[(*E*)-2-(trimethylsilyl)ethenyl]-1*H*-benzotriazole **6.9.**

An interesting, but not unexpected result was obtained upon the alkylation of **6.4** with $ICH_2SiMe_3$. After the initial formation of 1-(1*H*-benzotriazol-1yl)-2-(trimethylsilyl)ethyl phenyl sulfoxide, the β-elimination of $PhSO^-$ under basic conditions gave the corresponding 1-[(*E*)-2-(trimethylsilyl)ethenyl]-1*H*-benzotriazole **6.9**. The *anti* position is favored and the elimination of will give only the *trans* product **6.9**.

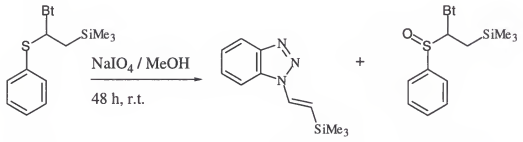



Scheme 6.17

Previously, Hofmann and co-workers observed that arylalkyl sulfoxides undergo base-catalyzed 1,3-rearrangements and subsequent β–eliminations to stilbene derivatives and studied the mechanistic aspects of b-eliminations in DMSO [64JACS1561]. The kinetic and isotope exchange experiments place these eliminations in the E2 category (Scheme

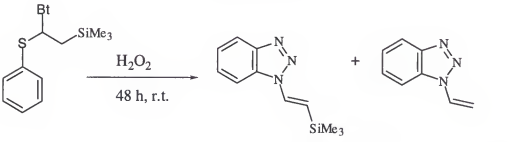
6.17). The exact degree of bond scission in the transition state is difficult to evaluate, but it is likely that the $PhSO^-$ group has started to leave before the β-C-H bond has been completely broken.

The same elimination is observed when the intermediate sulfoxide **6.7c** is obtained via the oxidation of 1-(1*H*-benzotriazol-1yl)-2-(trimethylsilyl)ethyl phenyl sulfide **6.8** prepared using a method previously reported in our group [97MI1]. The nature of by-products depends on the reaction conditions.




**6.8** **6.9** (40%) **6.7c** (40%)

Scheme 6.18



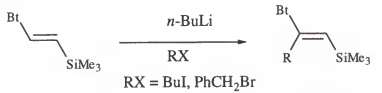

**6.8** **6.9** (65%) **6.10** (10%)

Scheme 6.19

The synthesis of compound **6.9** has been optimized: the intermediate **6.7c** was completely converted into the final product.

6.2.6 Alkylation of 1-[(*E*)-2-(trimethylsilyl)ethenyl]-1*H*-benzotriazole **6.9**.

Lithiation of compound **6.9** with *n*-BuLi followed by reaction with an alkyl halide gave the expected substitution products **6.11a**,**b**.



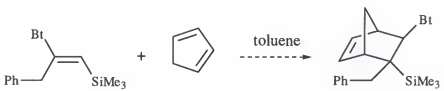

**6.9** **6.11a**,**b**

**a**: R = Bu
**b**: R = $PhCH_2$

Scheme 6.20

6.2.7. Attempted Diels-Alder reaction of **6.9** with cyclopentadiene.

Freshly distilled cyclopentadiene was added to a toluene solution of **6.11b** at -40°C under stirring and the reaction mixture was allowed to slowly reach r.t.. The GC trace of samples collected at various times from the reaction showed only the presence of starting materials. The reaction mixture was heated to reflux for 36 h and monitored by GC, but no products were detected. As previously reported [84T2585] the method might require the use of a catalyst (Lewis acid) or heating the reagents in a sealed tube [84JOC3235].




**6.11b**

Scheme 6.21

6.2.8. The fluoride-induced elimination of silicone from **6.11b** was attempted using CsF or TBAF in refluxing $CH_2Cl_2$ or using CsF in DMF at 80°C, but the GC trace showed only the starting material.

## 6.3 Conclusions

Since previous studies of sulfoxide alkylation have drawn contradictory conclusions, our experiments aimed to bring more data to the problem. It can be concluded that: (I) there is no diastereselectivity (or very low d.e.) for alkyl methyl sulfoxide alkylation; (ii) the presence of a bulkier group like phenyl improves the d.e., especially when the lithiation is carried out in the presence of the electrophile. The studies involving racemic sulfoxides could be extrapolated to enantiomerically pure sulfoxides.

## 6.4 Experimental Part

### General Procedure for the Synthesis of Compounds **6.2a,b.**

To a solution of α-benzotriazol-1-yldimethyl sulfide or α-benzotriazol-1-ylmethyl isopropyl sulfide (19mmol) in methanol (10ml) was added a 30% aqueous solution of $H_2O_2$ (2 ml) and the resulting solution was stirred at r.t. for 24 h. After addition of $CH_2Cl_2$ (100 ml) the resulting organic layer was dried ($Na_2SO_4$) and evaporated in vacuo.

α-Benzimidazol-1-yldimethyl sulfoxide (**6.2a**).

Yield 90%, m.p. 140-141°C; $\delta_H$ ($CDCl_3$): 8.07 (d, $J$ = 8.4 Hz, 1H), 7.75 (d, $J$ = 8.4 Hz, 1H), 7.55 (t, $J$ = 6 Hz, 1H), 7.42 (t, $J$ = 7.8 Hz, 1H), 5.83 (d, $J$ = 13.7 Hz, 1H), 5.65 (d, $J$ = 13.7 Hz, 1H), 2.81 (s, 3H); $\delta_C$ ($CDCl_3$): 145.6, 133.8, 128.6, 124.7,

119.8, 110.2, 65.4, 36.3. Anal. Calcd for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52. Found: C, 49.37; H, 4.66; N, 21.58.

α-Benzimidazol-1-ylmethyl isopropyl sulfoxide (**6.2b**).

Yield 90%, m.p. 95-96°C; $\delta_H$ ($CDCl_3$): 8.07 (d, $J$ = 8.1 Hz, 1H), 7.77 (d, $J$ = 8.1Hz, 1H), 7.54 (t, 7.2 Hz, 1H), 7.41 (t, $J$ = 7.5 Hz, 1H), 5.83 (d, $J$ = 13.8 Hz, 1H), 5.63 (d, $J$ = 13.8 Hz, 1H), 2.88-2.83 (m, 1H), 1.43-1.35 (m, 6H); $\delta_C$ ($CDCl_3$): 145.8, 134.0, 128.5, 124.6, 119.9, 110.4, 62.3, 48.9, 16.0, 14.3. Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.55; H, 6.01; N, 18.78.

1*H*-Benzotriazol-1ylmethyl phenyl sulfide (**6.3**).

Thiophenol (7.98 g, 77.84 mmol, 1.3 equiv) and chloromethyl-1-benzotriazole (10.00 g, 59.88 mmol, 1 equiv) were added to a solution of MeONa (3.23 g, 59.88 mmol, 1 equiv, from 1.37 g Na) in methanol (250 ml) and the resulting solution refluxed for 4 h. The reaction mixture was cooled to r.t., the solvent evaporated and the residue was dissolved in $CH_2Cl_2$. The organic solution was washed with NaOH aqueous solution 10% (2 × 50 ml),then with $H_2O$ (2 × 50 ml), dried ($Na_2SO_4$) and the crude product recrystallized from MeOH. Yield 75%, m.p. 95-96°C; $\delta_H$ ($CDCl_3$): 8.02 (d, $J$ = 9.0 Hz, 1H), 7.40-7.18 (m, 8H), 5.92 (s, 2H); $\delta_C$ ($CDCl_3$): 146.2, 132.9, 132.1, 129.2, 128.6, 127.3, 124.0, 120.0, 110.0, 52.6. Anal. Calcd for $C_{13}H_{11}N_3S$: C, 64.70 ; H, 4.59; N, 17.41. Found: C, 64.40; H, 4.54; N, 17.37.

1*H*-Benzotriazol-1ylmethyl phenyl sulfoxide (**6.4**).

To a solution of 1-(phenylthiomethyl)benzotriazole (7.96 g, 33 mmol) in methanol (400 ml) was added a solution of $NaIO_4$ (10.65 g, 50 mmol) in water (100 ml). The

resulting solution was stirred at r.t. for 24 h. After concentration of the solvent, the residue was treated with $CH_2Cl_2$ (200 ml). NaI was filtered off and the resulting organic layer was dried ($Na_2SO_4$) and evaporated in vacuo. Yield 70%, m.p. 146-147°C; $\delta_H$ (DMSO): 8.03 (d, $J$ = 9.0 Hz, 1H), 7.75 (d, $J$ = 6.0 Hz, 1H), 7.27-7.55 (m, 7H), 6.20 (dd, $J_1$ = 15.0 Hz, $J_2$ = 63.0 Hz, 2H); $\delta_C$ (DMSO): 144.8, 140.6, 133.7, 131.6, 129.2, 127.6, 124.6, 124.3, 119.0, 111.3, 67.4. Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.81; H, 4.25; N, 16.41.

1*H*-Benzotriazol-1ylmethyl phenyl sulfone (**6.5**).

To a solution of α-benzotriazol-1-yl methyl phenyl sulfide (19mmol) in methanol (10ml) was added a 30% aq. sol. of $H_2O_2$ (2ml) and the resulting solution was stirred at r.t. for 24 h. After addition of $CH_2Cl_2$ (100ml) the resulting organic layer was dried ($Na_2SO_4$) and evaporated in vacuo. Yield 85%, m.p. 195-196°C; $\delta_H$ (DMSO): 8.06 (d, $J$ = 9.0 Hz, 1H), 7.77-7.40 (m, 8H), 6.72 (s, 2H); $\delta_C$ (DMSO): 144.8, 140.6, 133.7, 131.6, 129.2, 127.6, 124.6, 124.3, 119.0, 111.3, 67.4. Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.04; H, 3.67; N, 15.42.

General procedure for the synthesis of compounds **6.6a-c** and **6.7a,b**.

A solution of 1*H*-benzotriazol-1ylmethyl alkyl or aryl sulfoxide (**6.2a,b** or **6.4**) (1 equiv) in THF (50ml) under argon atmosphere was cooled to -78 ° C and the electrophile (1.1 equiv) was added. LDA (1.1 equiv, 1.5 M n-hexane solution) was added slowly dropwise. The resulting suspension was kept at -78° C for 2 h then at r.t. overnight. The reaction mixture was quenched with $NaHCO_3$, extracted with ether, dried over $Na_2SO_4$ and the solvent removed to give the crude product. The crude product was purified by column chromatography eluent EtOAc : $Et_2O$ = 1 : 2.

1–(1*H*-Benzotriazol-1yl)ethyl methyl sulfoxide **6.6a.**

Substrate: **6.2a**. Electrophile: MeI. Yield 85%, mixture of diastereomers A : B = 1 : 2, m.p. 98-100°C; $\delta_H$ ($CDCl_3$): 8.07-8.09 (m, 1H, A+B), 7.86 (d, *J* = 9.0 Hz, 1H, B), 7.74 (d, *J* = 9.0 Hz, 1H, A), 7.55-7.50 (m, 1H, A+B), 7.43-7.39 (m, 1H, A+B), 5.90-5.80 (m, 1H, A+B), 2.40 (s, 3H, B), 2.40 (s, 3H, B), 2.22 (d, *J* = 9.0 Hz, 3H, B). 2.15 (d, *J* = 9.0 Hz, 3H, A); $\delta_C$ ($CDCl_3$): 145.9 (B), 145.7 (A), 133.0 (B), 133.0 (A), 127.8 (B), 127.8 (A), 124.3 (B), 124.3 (A), 119.7 (A), 119.6 (B), 11.2 (B), 110.3 (A), 71.9 (A), 71.3 (B), 34.6 (B), 34.5 (A), 13.0 (A), 12.9 (B). Anal. Calcd for $C_9H_{11}N_3OS$: C, 51.65; H, 5.30; N, 20.08. Found: C, 51.25; H, 5.34; N, 19.81.

1–(1*H*-Benzotriazol-1yl)but-3-enyl methyl sulfoxide **6.6b.**

Substrate: **6.2a**. Electrophile: allyl bromide. Yield 65%, mixture of diastereomers A : B = 1 : 1.7, oil; $\delta_H$ ($CDCl_3$): 8.08 (d, *J* = 9.0 Hz, 1H, B), 8.07 (d, *J* = 6.0 Hz, 1H, A), 7.94 (d, *J* = 9.0 Hz, 1H, A), 7.77 (d, *J* = 6.0 Hz, 1H, B), 7.54 (t, *J* = 9.0 Hz, 1H, A), 7.52 (t, *J* = 6.0 Hz, 1H, B), 7.41 (t, *J* = 9.0 Hz, 1H, B), 7.39 (t, *J* = 6.0 Hz, 1H, A), 5.91-5.83 (m, 1H, A+B), 5.76-5.61 (m, 1H, A+B), 5.21-5.00 (m, 2H, A+B), 3.50-3.25 (m, 2H, A+B), 2.44 (s, 3H, B), 2.38 (s, 3H, A); $\delta_C$ ($CDCl_3$): 145.9 (A), 145.5 (B), 133.4 (B), 133.0 (A), 130.2 (A) ,130.2 (B), 128.0 (B), 127.9 (A), 124.3 (B), 124.2 (A), 120.0 (A), 119.8 (B), 119.7 (B), 119.6 (A), 111.6 (A), 109.9 (B), 75.5 (B), 74.8 (A), 34.9 (B), 34.7 (A), 31.7 (B), 31.1 (A). Anal. Calcd for $C_{11}H_{13}N_3OS$: H, 5.57; N, 17.86. Found: H, 5.61; N,16.34.

1–(1*H*-Benzotriazol-1yl)ethyl isopropyl sulfoxide **6.6c.**

Substrate: **6.2b**. Electrophile: MeI. Yield 80%, oil; $\delta_H$ ($CDCl_3$): 8.06-7.93 (m, 2H), 7.51-7.35 (m, 2H), 6.04 (q, *J* = 9.0 Hz, 1H), 2.44-2.35 (m, 1H), 2.18 (d, *J* = 9.0 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H); $\delta_C$ ($CDCl_3$): 146.0, 133.0,

127.8, 124.2, 119.5, 112.3, 68.6, 48.0, 15.8, 14.8. Anal. Calcd for $C_{11}H_{15}N_3OS$: C, 56.67; H, 6.37; N, 17.71. Found: C, 54.70; H, 6.55; N, 17.30.

1-(1*H*-Benzotriazol-1yl)ethyl phenyl sulfoxide **6.7a.**

Substrate: **6.4**. Electrophile: MeI. Yield 69%, m.p. 113-115°C; $\delta_H$ ($CDCl_3$): 8.01 (d, *J* = 6.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.50-7.25 (m, 7H), 5.77 (q, *J* = 6.6 Hz, 1H), 2.11 (d, *J* = 6.6 Hz, 3H); $\delta_C$ ($CDCl_3$): 145.9, 139.2, 133.3, 132.1, 129.0, 127.8, 124.7, 124.3, 119.9, 110.9, 74.8, 13.2. Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.04; H, 4.76; N, 15.32.

1-(1*H*-Benzotriazol-1yl)pentyl phenyl sulfoxide **6.7b.**

Substrate: **6.4**. Electrophile: BuI. Yield 73%, mixture of diastereomers A : B = 1 : 2, m.p. 99-100°C; $\delta_H$ ($CDCl_3$): 8.01-7.96 (m , 2H, A+B), 7.71 (d, *J* = 9.0 Hz, 1H, A), 7.46-7.15 (m, 15H, A+B), 5.68-5.63 (m, 1H, A), 5.39-5.34 (m, 1H, B), 2.86-2.51 (m, 4H, A+B), 1.43-1.17 (m, 8H, A+B), 0.83 (t, *J* = 6.0 Hz, 3H, A), 0.81 (t, *J* = 9.0 Hz, 3H, B); $\delta_C$ ($CDCl_3$): 154.6 (A), 145.4 (B), 140.0 (B), 139.2 (A), 133.2 (B), 133.2 (A), 131.8 (B), 131.6 (A), 128.7 (B), 128.7 (A), 127.7 (B), 127.5 (A), 124.2 (B), 124.1 (A), 124.1 (B), 124.0 (A), 119.7 (B), 119.6 (A), 111.0 (A), 109.1 (B), 80.1 (B), 79.4 (A), 27.7 (A), 27.6 (B), 27.4 (B), 27.2 (A), 21.7 (B), 21.7 (A), 13.4 (B), 13.4 (A). Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 65.36; H, 6.39; N, 13.52.

1-(1*H*-Benzotriazol-1yl)-2-(trimethylsilyl)ethyl phenyl sulfide **6.8.** was prepared according to a procedure previously reported [97MI1].

1-[(*E*)–2–(Trimethylsilyl)ethenyl]–1*H*-benzotriazole **6.9**.

A solution of 1*H*-benzotriazol-1ylmethyl phenyl sulfoxide (1 equiv) in THF (50ml) under argon atmosphere was cooled to -78 ° C and *n*-BuLi (1.1 equiv, 1.5 M *n*-hexane solution) was added slowly dropwise. The resulting suspension was kept at -78°C for 2h then iodomethyltrimethylsilane (1.1 equiv) was added. The resulting suspension was kept at -78° C for 2 h then at r.t. overnight. The reaction mixture was quenched with $NaHCO_3$, extracted with ether, dried over $Na_2SO_4$ and the solvent removed to give the crude product. The crude product was purified by column chromatography eluent EtOAc : $Et_2O$ = 1 : 2. Yield 50%.

The same product was obtained using the following procedure: to a solution of 1-(1*H*-benzotriazol-1yl)-2-(trimethylsilyl)ethyl phenyl sulfide (**6.8**) (33 mmol) in methanol (400 ml) was added a solution of $NaIO_4$ (50 mmol) in water (100 ml). The resulting solution was stirred at r.t. for 24 h. After concentration of the solvent, the residue was treated with $CH_2Cl_2$ (200 ml). NaI was filtered off and the resulting organic layer was dried ($Na_2SO_4$) and evaporated in vacuo. The crude product was purified by column chromatography eluent EtOAc : $Et_2O$ = 1 : 2. Yield 40%, m.p. 45-46°C; $\delta_H$ ($CDCl_3$): 8.19 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.71 (s, 1H), 7.65 (t, *J* = 9.0 Hz, 2H), 7.51 (t, *J* = 9.0 Hz, 1H), 5.61 (d, *J* = 24.0 Hz, 1H), 0.38 (s, 9H); $\delta_C$ ($CDCl_3$): 146.4, 132.6, 131.0, 128.1, 124.4, 120.1, 117.0, 110.4, -1.3. Anal. Calcd for $C_{11}H_{15}N_3Si$: C, 60.79; H, 6.96; N, 19.33. Found: C, 61.17; H, 7.12; N, 19.16.

General Procedure for the Synthesis of Compounds **6.11a,b**.

A solution of (*E*)–2–(1*H*-benzotriazol-1yl)-1-trimethylsilylethene (0.21 g, 1 mmol, 1 equiv) in THF (50ml) under argon atmosphere was cooled to -78 ° C and *n*BuLi (0.82 ml, 1.1 mmol, 1.41 M) was added slowly dropwise. The resulting suspension was kept at -78° C for 1 h and then the appropriate electrophile (1.1 mmol, 1.1 equiv) was added. The

resulting suspension was kept at -78° C for 2 h then at r.t. overnight. The reaction mixture was quenched with NaCl, extracted with ether, dried over $Na_2SO_4$ and the solvent removed to give the crude product.

1–[(*E*)–1–Butyl-2–(trimethylsilyl)ethenyl]–1*H*-benzotriazole **6.11a**. Electrophile used: BuI. Yield 90%, oil; $\delta_H$ ($CDCl_3$): 8.06 (d, *J* = 6.0 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.48 (t, *J* = 0.6 Hz, 1H), 7.36 (t, *J* = 6.0 Hz, 2H), 5.75 (s, 1H), 2.93-2.98 (m, 2H), 1.29-1.30 (m, 4H), 0.80 (t, *J* = 6.0 Hz, 3H), 0.27 (s, 9H); $\delta_C$ ($CDCl_3$): 149.0, 146.1, 132.2, 127.6, 124.0, 120.3, 120.0, 111.2, 34.1, 30.1, 22.4, 13.7, 0.0. Anal. Calcd for $C_{15}H_{23}N_3Si$: C, 65.88; H, 8.48; N, 15.37. Found: C, 65.91; H, 8.66; N, 15.40.

1–[(*E*)–1–Benzyl-2–(trimethylsilyl)ethenyl]–1*H*-benzotriazole **6.11b**. Electrophile used: $PhCH_2Br$. Yield 60%, oil; $\delta_H$ ($CDCl_3$): 7.70 (d, *J* = 9.0 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.18 (t, *J* = 6.0 Hz, 1H), 7.03 (t, *J* = 6.0 Hz, 1H), 6.77-6.91 (m, 5H),5.73 (s, 1H), 4.14 (s, 2H), 0.08 (s, 9H); $\delta_C$ ($CDCl_3$): 146.4, 146.1, 136.6, 132.1, 128.3, 128.1, 127.7, 126.5, 123.9, 122.1, 120.0, 111.0, 39.6, 0.0. Anal. Calcd for $C_{18}H_{21}N_3Si$: H, 6.88; N, 13.67. Found: H, 6.63; N, 13.34.

# CHAPTER 7

## GENERAL CONCLUSIONS

Although the work presented in Chapter 2 is not directly connected with the aspects of chiral synthesis, it provides the methodology for the synthesis of new bismethylenebenzazoles, sterically hindered heterocyclic systems with considerable preparative potential.

Hopefully, the study of selective reactivity of $sp^2$ and $sp^3$-carbanions of 1-substituted 1,2,4-triazoles presented in Chapter 3, fills a void in the analysis of 1,2,4-triazole alkylation chemistry.

Stereochemical control is one of the most important aspects in modern organic synthesis. The generation of new chiral centers in a target molecule is achieved either through addition to one of the two stereoheterotopic faces of a double bond (e.g. in a chiral ketone like fenchone) or by selective substitution of stereoheterotopic ligands (e.g. in chiral methylenesulfoxides).

The work described in Chapters 4 and 5 includes projects that address specifically these two aspects of enantioselective and diastereoselective synthesis.

1,2,4-Triazole and benzimidazole mediated asymmetric syntheses exemplify the concept of "self-regeneration of stereogenic centers" using these two heterocyclic systems as the required conformationally rigid templates. Thus, novel spirobicyclic benzimidazoles, oxazolobenzimidazoles and 2-($\alpha$-hydroxyalkyl)benzimidazoles were obtained with excellent diastereoselectivity.

Many natural or synthetic biologically active compounds contain a sulfoxide functional group. Chiral sulfoxides are gaining considerable importance as chiral synthons for asymmetric C-C bond formation. Nevertheless, due to the limited number of practical synthetic methods, the development of enantiomerically and diastereomerically pure sulfoxides in the pharmaceutical industry has been relatively scarce. Chapter 6 includes the first steps toward the study of asymmetric alkylation of benzotriazol-1-ylmethyl sulfoxides.

The author is grateful to Dr. Peter Steel (University of Canterbury, Christchurch, New Zealand) for providing all the X-ray crystal structures, to Dr. Ion Ghiviriga (University of Florida) for his advice regarding the 2D- and NOE NMR experiments and also to the Elemental Analysis service team at the University of Florida.

## REFERENCES

The reference citation system employed throughout this dissertation is that from "Comprehensive Heterocyclic Chemistry II" Pergamon Press, 1996 (Eds. Katritzky, A. R.; Rees, C. W. and Scriven, E.)

Each time a reference is cited, a number and letter code appear in brackets, for example 00ABC000. The first two digits denote the year of the twentieth century, the letter code is an abbreviation for the journal or book cited and the last digits represent the page number. Additional notes to this reference system are as follows:

(ii) References are listed consecutively by year, alphabetically by the journal code and then by page number.

(ii) Each reference code is followed by the conventional literature citation complete with the name of the authors.

(iii) Journals which are published in more than one part, or more than one volume per year, include in the abbreviation cited the appropriate part or volume number.

(iv) Books and journals which are less commonly used are called "MI" for miscellaneous.

28JCS2393 Philips, M.A., *J. Chem. Soc.* **1928**, 2393.

43OSC65 Wagner, E.C. and Millett, W.H., *Org. Synth. Coll. Vol.* **1943**, II, 65.

44JBC225 Wolley, D.W., *J. Biol. Chem.* **1944**, 152, 225.

47JCS1619 Rogers, M.A.T. and Sexton, W.A., *J. Chem. Soc.* **1947**, 1619.

49JOC790 Emerson, W.S. and Patrick, T.M. Jr., *J. Org. Chem.* **1949**, 14, 790.

53CA11327 Tamm, I., Folkers K. and Horsfall, F.L., *J. Exptl. Med.* **1953**, 98, 219; *Chem. Abstr.*, **53**,(11327).

55JOC225 Shirley, D. A.; Gross, B. H.; Roussel, P. A. *J. Org. Chem.* **1955**, *20*, 225.

57JACS427 Hein, D.W., Alheim, R-J., Leavitt, J.J., *J. Amer. Chem. Soc.* **1957**, 79, 427.

57JCS5706 Wang, L., Joullie, M.M., *J. Amer. Chem. Soc.* **1957**, 79, 5706.

58JCS2021 Bunnett, J.F., Hrutfiord, B.F, *J. Am. Chem. Soc.* **1958**, 83, 2021.

58CA9048 Zil'Berman, E.N. et. al., *Zur. Russ. Fiz-Chim* **1962**, 32, 3039. *Chem. Abstr.*, **58**, (9048).

61CR87 Potts, K. T. *Chem. Rev.* **1961**, *61*, 87.

61JOC274 Jenkins, G.L., Knevel, A.M. and Davis, C.S., *J. Org. Chem.* **1961**, 26, 274.

61JOC3434 Rai, C., and Braunwarth, J.B., *J. Org. Chem.* **1961**, 26, 3434.

63JCS4322 Cossey, H.D., Sharpe, C.J. and Stephens, J.J., *J. Chem. Soc.* **1963**, 4322.

64JACS1561 Hofmann, J.E.; Wallace, T.J.; Schriesheim, A. *J. Am. Chem. Soc.* **1964**, 1561.

64MI Harmer, F.M., "The Chemistry of Heterocyclic Compounds", Ed. Weissenberger A., Interscience, New York, 1964, vol. 18, Ch.6.

64N639 Kadin S. B.; Eggers H. J.; Tamm I. *Nature* **1964**, *201*, 639.

65TL2365 Hideg, K., Hankovsky, H.O., *Tet. Lett.* **1965**, 2365.

68CA68992 Wagner A. F.; Folkers K. A. *Chem. Abstr.* **1968**, *68*, 68992j.

69N785 Tamm I.; Eggers H. J.; Bablanian R.; Wagner A. F.; Folkers K. *Nature* **1969**, *223*, 785.

71JACS3077 Durst, T., Viau, R., McClory, M.R. *J. Am. Chem. Soc.* **1971**, 3077.

72CA34326 Tertov B. A.; Koblik A. V.; Avdyunina N. I. *Chem. Abstr.* **1972**, *76*, 34326v.

72TL4839 Nishihata, K., Nishio, M., *Tetrahedron Letters* **1972**, 47, 4839.

73CA137156 Fauran C.; Eberle J.; Le Cloarec A. Y.; Raynaud G.; Dorme N. *Chem. Abstr.* **1973**, *79*, 137156f.

74CR279 Preston P. N. *Chem. Rev.* **1974**, *74*, 279.

75TL3519 Dryanska, V., Ivanov, C., *Tetrahedron Letters* **1975**, 41, 3519.

76S730 Spitulnik, M.J., *Synthesis* **1976**, 730.

76CA135655 Fauran C.; Turin M.; Raynaud G.; Sergant M. *Chem. Abstr.* **1976**, *84*, 135658x.

77ACS203 Perregard, J. and Lawesson, S.O., *Acta. Chem. Scand.* **1977**, 31, 203.

77S892 Rossini, G. and Medici, A., *Synthesis* **1977**, 892.

77TL4009 Farnum, D.G et al. *Tetrahedron Lett.* **1977**, *46*, 4009.

78CL1253 Mukaiyama T.; Sakito Y.; Asami M. *Chem. Lett.* **1978**, 1253.

78JIC531 Dubey, P.M. and Ratnam, C.V., *J. Indian. Chem. Soc.* **1978**, 16, 531.

78JOC2296 Boger, D.L., *J. Org. Chem.* **1978**, 43, 2296.

79AJC2441 Coxon J.M.; Steel P.J. *Aust. J. Chem.* **1979**, *32*, 2441.

79JCS260 Pramasivam, R., Palaniappan, R. and Ramkrishnan, V.T., *J. Chem. Soc.* **1979**, 260.

79JCS(P1)2845 Chadwick, D. J.; Cliffe, I. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2845.

79JHC13 Cohen, V.I., *J. Heterocycl. Chem.* **1979**, 16, 13.

79TL2649 Kocienski, P.J. *Tetrahedron Lett.* **1979**, *28,* 2649.

80BCS5288 Davis, F.A., Ulatowski, T.G., Haque, M.S., *Bull. Chem Soc. Jpn.* **1980**, *53(5),* 1414.

80JOM141 Gasparini, J. P.; Gassend, R.; Maire, J. C.; Elguero, J. *J. Organometall. Chem.* **1980**, *188*, 141.

81SC1025 Drabowicz, J., Mikolajczyk, M. *Synth. Comm.* **1981**, *11(12),* 1025.

81T4111 Mukaiyama T. *Tetrahedron* **1981**, *37*, 4111.

81TL4643 Paquette, L.A., Williams, R.V. *Tetrahedron Lett.* **1981**, *22(46),* 4643.

82LA1387 Humburg, G.; Mildenberger, H. *Liebigs Ann. Chem.* **1982**, 1387.

84JOC3235 Hayama, T., Tomoda, S., Takeuchi, Y., Nomura, Y. *J. Org. Chem.* **1984**, *49* , 3235.

84MI1 Polya, J. B., *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford; 1984, Vol. 5, p 733.

84S145 Osuka, A., Uno, Y., Horiuchi H., Suzuky, H., *Synthesis* **1984**, 145.

84T2585 De Lucchi, O., Modena, G. *Tetrahedron* **1984**, *40(14),* 2585.

84TL1049 Pitchen, P., Kagan, H.B. *Tetrahedron Lett.* **1984**, *25(10),* 1049.

84TL1753 Young, R.N., Gauthier, J.Y., Coombs, W. *Tetrahedron Lett.*, **1984**, *25(17),* 1753.

84TL4113 Demailly, G., Greck, C., Solladie, G. *Tetrahedron Lett.* **1984**, *37*, 4113.

85MI1 Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985.

85S302 Cuberes, M. R.; Moreno-Manas, M.; Trius, A. *Synthesis* **1985**, 302.

85TL4763 Imamoto T.; Takiyama N.; Nakamura K. *Tetrahedron Lett.* **1985**, *26*, 4763.

86CA22645 Zhang, H.; Liao, L.; Guo, Q. *Youji Huaxue* **1986**, 108; *Chem. Abstr.* ***1986, 105,*** 226456b.

86JHC1257 Anderson D. K.; Sikorski J. A.; Reitz D. B.; Pilla L. T. *J. Heterocycl. Chem.* **1986**, *23*, 1257.

87CA18565 Jpn. Kokai Tokkyo Koho JP 61,145,165 *Chem. Abstr.* **1987**, *106*, 18565e.

87JCS(P1)781 Katritzky, A.R.; Rachwal, S.; Caster, K.C. *J. Chem. Soc. Perkin I* **1987**, 781.

87JCS(P1)2787 Atkinson R. S.; Tughan G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2787.

87JOC1414 Nakamura, K.; Higaki, M.; Adachi, S.; Oka, S.; Ohno, A. *J. Org. Chem.* **1987**, *52*, 1414.

88CA75308 Zhang, H.; Liao, L.; Guo, Q. *Ziran Kexueban* **1987**, 26(3), 341; *Chem. Abstr.* **88**, (75308).

88H1975 Chimirri A.; Grasso S.; Romeo G.; Zappalà M. *Heterocycles* **1988**, *27*, 1975.

88JOC5685 Katritzky A. R.; Rewcastle G. W.; Fan W.-Q. *J. Org. Chem.* **1988**, *53*, 5685.

89JOC2663 Pyne, S.G., Boche G. *J. Org. Chem.* **1989**, *54*, 2663.

89JOC2949 Katritzky A. R.; Akutagawa K. *J. Org. Chem.*, **1989**, *54*, 2949.

90AC(A)467 Sheldrick G.M. *Acta Crystallogr. Sect.A* **1990**, *46*, 467.

90H1245 Hussain S. A.; Sarfaraz T. B.; Sultana N.; Murtaza N.; Qureshi I. H. *Heterocycles* **1990**, *31*, 1245.

90H2029 Ohta S.; Maruyama A.; Kawasaki I.; Hatakeyama S.; Ichikawa M.; Guro T. *Heterocycles* **1990**, *31*, 2029.

90JHC673 Moreno-Manas, M.; Bassa, J.; Llado, N.; Pleixats, R. *J. Heterocycl. Chem.* **1990**, *27*, 673.

90SC955 Yadagiri, B. and Lown, J.W., *Synth. Commun.* **1990**, 20(7), 955.

90T633 Katritzky A. R.; Jozwiak A.; Lue P.; Yannakopoulou K.; Palenik G. J.; Zhang Z.-Y. *Tetrahedron* **1990**, *46*, 633.

90T641 Katritzky, A. R.; Lue, P; Yannakopoulou, K. *Tetrahedron* **1990**, *46*, 641.

91JHC653 Melendez, E., Merchan, F.L., Merino, P., Orduna, J. and Urchegui, R., *J. Heterocycl. Chem.* **1991**, 28(3), 653.

91MI Silverstein, R.M., Bassler, G.C. and Morrill, T.C., "Spectrometric Identification of Organic Compounds", Fifth Ed., Ed. John Wiley, New York, 1991, 165.

91SC625 Ares, J.J., *Synth. Commun.* **1991**, 21(5), 625.

92LA843 Katritzky, A. R.; Li, J.; Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843.

93AHC208 Rewcastle, G. W.; Katritzky, A. R. *Adv. Het. Chem.* **1993**, *56*, 208.

93MI1 Sheldrick G.M. *SHELXL-93*, University of Gottingen 1993.

94CI636 Pitchen, P. *Chem. and Ind.* **1994***11(12),* 636.

| | |
|---|---|
| 94H1367 | Diez-Barra, E.; de la Hoz, A.; Loupy, A.; Sanchez-Migallon, A. *Heterocycles* **1994**, *38*, 1367. |
| 94JCS(CC)1739 | Williams, R.V., Chauhan, K., Gadgil, V.R. *J. Chem. Soc. Chem. Comm.* **1984**, 1739-1740. |
| 94JOC2033 | Doyon J.; He W.; Paquette L. A. *J. Org. Chem.* **1994**, *59*, 2033. |
| 94MI1 | Eliel, L.E.; Wilen, S.H., "Stereochemistry of Organic Compounds", Wiley-Interscience, New York, 1994. |
| 94TL6713 | Dimitrov V.; Bratovanov S.; Simova S.; Kostova K. *Tetrahedron Lett.* **1994**, *35*, 6713. |
| 95CA31406 | Chimirri A.; Grasso S.; Monforte A. M.; Monforte P.; Zappalà M. *Chem. Abstr.* **1995**, *122*, 31406d. |
| 95CA313807 | Chimirri A.; Grasso S.; Monforte A. M.; Monforte P.; Zappalà M. *Chem. Abstr.* **1995**, *123*, 313807g. |
| 95CR1717 | Carreno, M.C. *Chem. Rev.* **1995**, 95, 1717. |
| 95JOC1244 | Katritzky, A. R.; Oniciu, D. C.; Serdyuk, L.; Ghiviriga, I. *J. Org. Chem.* **1995**, *60*, 1244. |
| 95JOC3401 | Katritzky, A. R.; Li, J., Stevens, C. *J. Org. Chem.* **1995**, *60*, 3401. |
| 95JOC5638 | Katritzky, A.R., Chen, J. and Yang, Z., *J. Org. Chem.* **1995**, 60, 5638. |
| 95MI1 | Solladie, G., Carreno, M.C. *Organosulphur Chemistry. Synthetic Aspects* , Academic Press, New York, 1-47, 1995. |
| 95TL6537 | Barros, M.T., Leitao, A.J., Maycock, C.D. *Tetrahedron Lett.* **1995**, *36,* 6537. |
| 96AG2708 | Seebach, D., Sting, A.R., Hoffmann, M., *Angew. Chem. Ed. Eng.* **1996**, *35*, 2708. |
| 96COS125 | Richardson K. *Contemp. Org. Synth.* **1996**, *3*, 125. |

96MI1 Garratt, P. J. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford; 1996, Vol. 4, p 127.

96TA1621 Katritzky A. R.; El-Zemity S. R.; Leeming P.; Hartshorn C. M.; Steel P. J. *Tetrahedron: Asymmetry* **1996**, *7*, 1621.

96TA1631 Katritzky A. R.; Wang J.; Leeming P.; Steel P. J. *Tetrahedron: Asymmetry* **1996**, *7*, 1631.

96TL8929 Bulman Page, P.C., Purdle, M., Lathbury, D. *Tetrahedron Lett.* **1996**, *37(49),* 8929.

97CR721 Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, *97*, 721.

97JOC706 Katritzky, A. R.; Feng, D.; Lang H. *J. Org. Chem.* **1997**, *62*, 706.

97JOC715 Katritzky, A. R.; Feng, D.; Lang H. *J. Org. Chem.* **1997**, *62*, 715.

97MI1 Toader, D. Ph. D. thesis, University of Florida, 1997.

97SC1111 Grigg, R., Najera, C., Sansano, J.M., Yus, M. *Synthetic Comm.* **1997**, *27(6),* 1111.

97TA1491 Katritzky, A. R.; Aslan, D. C.; Leeming, P.; Steel, P. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1491.

97TL5047 Barros, M.T., Leitao, A.J., Maycock, C.D. *Tetrahedron Lett.* **1997**, *38(28),* 5047.

## BIOGRAPHICAL SKETCH

Diana Crimhilda Aslan was born on July 15, 1968, in Bucharest, Romania. She graduated in 1993 from the Polytechnic University in Bucharest with a Bachelor of Science degree with a major in organic chemistry and a minor in chemical engineering. From August 1993 to August 1994, she worked as a research assistant at the Organic Chemistry Department of the Polytechnic University in Bucharest .

In August 1994, she commenced the graduate program at the Department of Chemistry of the University of Florida under the supervision of Dr. Alan R. Katritzky. She obtained her Ph. D. degree in Chemistry in May 1998.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert J. Hanrahan
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John R. Reynolds
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Jonathan Eric Enholm
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Dinesh O. Shah
Charles A. Stokes Professor of Chemical Engineering

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 1998

Dean, Graduate School